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# GUNSHOT WOUNDS OF THE CHEST

## A REVIEW OF TWO HUNDRED AND EIGHTY CASES

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Gunshot wounds of the chest are a common problem of the military surgeon in active warfare, but they are frequently seen also in civil practice in large municipal hospitals. The same principles of therapy apply in both instances, but certain differences are at once apparent. During warfare, more emergency operations are performed; the septic complications are more frequent, and the mortality rate is somewhat greater. In civil practice, gunshot wounds are usually small; there is only a small amount of tissue damage; septic complications are uncommon; recovery is prompt, and the mortality rate is low provided the great vessels are not penetrated (if they are, rapid or immediate death is the rule). These differences are due largely to the penetrating missile. Penetration of the thorax as seen in patients admitted to large municipal hospitals is usually caused by plain or jacketed bullets. In warfare, on the other hand, penetration is often caused by shell fragments, which produce large wounds with extensive tissue damage and often necessitate early operation. With these wounds, septic complications are more numerous, and the mortality rate is somewhat higher. The type of septic complications and the end results are dependent to some extent on the virulence of the prevailing local organisms. Ranson [1] stated that the infections seen by him during the Chinese war appeared to be less virulent than those reported during the first World War.

The records of 280 cases of gunshot wounds of the chest have been reviewed in this series. All of the patients were admitted to Cook County Hospital during the nine year period from 1931 to 1939. To obtain a clear picture of thoracopulmonary wounds only, all cases have

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1. Ranson, F. T.: Notes on Gunshot Wounds of the Chest, J. Thoracic Surg. 9:278-290 (Feb.) 1940.

been deleted in which wounds of the heart or extrathoracic viscera obscured the clinical picture or influenced the course or the treatment of the chest wound.

### SUPERFICIAL GUNSHOT WOUNDS OF THE CHEST

There were 130 cases (46.4 per cent) in which there was no evidence that the pleural cavity had been entered by the projectile. Most of these patients had short periods of hospitalization and few serious complications. In 11 cases (7.8 per cent), some infection of the wound developed; this was relieved by incision and drainage or by hot wet dressings. In 1 case, however, an abscess of the chest wall extended into the pleural cavity and caused empyema which required resection of a rib and drainage.

Five patients (3.3 per cent) had simple or comminuted fracture of one rib. Fractured scapula was present in 1 case, and the clavicle was fractured in 1.

In this series there was 1 death due to tetanus. This patient had received 1,500 units of tetanus antitoxin on admission and was treated with large doses of antitoxin and avertin with amylene hydrate after the diagnosis was established. She died eighteen days after being shot.

### PENETRATING GUNSHOT WOUNDS OF THE CHEST

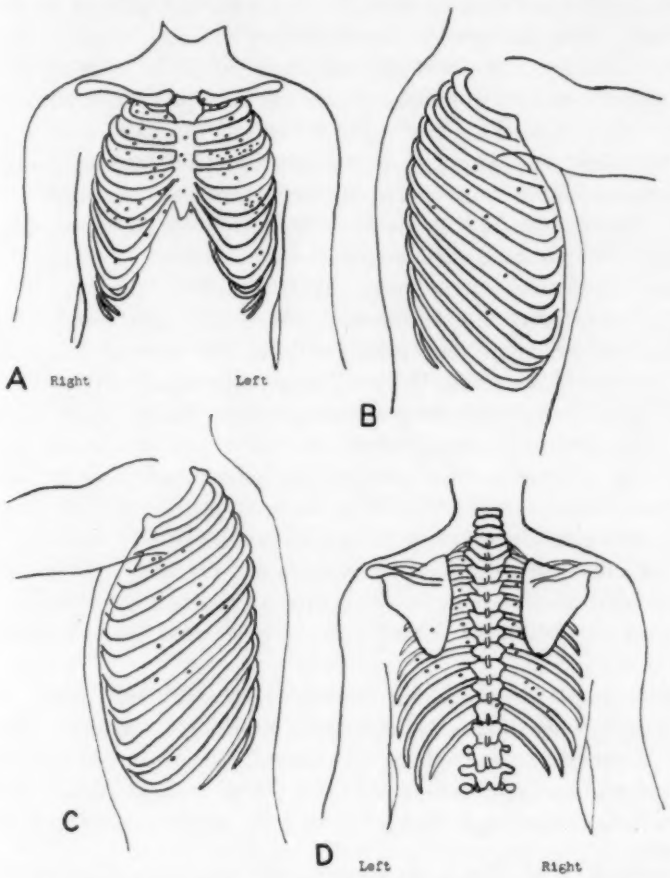
There were 150 patients (53.6 per cent) whose pleural cavity had been penetrated. Of these, 136 were admitted immediately after being shot, while 14 were admitted from forty hours to three weeks later, most of these coming from other hospitals. The wounds were caused by bullets of all the common calibers. There were 2 cases of shotgun wounds; one of these, in which the shot had been fired at close range, was the only case in which open sucking pneumothorax was present. In 78 cases (52 per cent) there was through and through penetration. There were 16 cases (10.6 per cent) in which multiple wounds were present and 5 (3 per cent) in which there was bilateral penetration.

### CLINICAL MANIFESTATIONS

Most of the patients admitted were in shock. This was variable but was considered severe in 45 (30 per cent) and moderate in 36 patients (24 per cent). In a few patients no shock was present. Dyspnea in varying degree and pain in the chest were common complaints. Hemoptysis occurred in 73 (48.7 per cent), but in many of these it was small in amount and did not recur.

*Subcutaneous Emphysema.*—Subcutaneous emphysema is a common finding with penetrating wounds of the chest. It was present in 61 (40.7 per cent) of the cases and was considered marked in 15 (10 per cent). None of these patients received any active therapy for emphysema.

Subcutaneous emphysema usually arises at the site of the wound either from air sucked in through the wound or from air extravasated from the pleural cavity or the lungs. A second form of emphysema, described by Berry,[2] is said to arise from a tear in the mediastinal pleura. In this form of emphysema air enters the mediastinum and ascends into the neck; from here it may extend in any direction in the




Wounds of entrance: *A*, in the anterior part of the chest; *B*, in the region of the right axilla; *C*, in the region of the left axilla; *D*, in the posterior part of the chest.

subcutaneous tissue. Occasionally, this causes such severe compression of the structures in the mediastinum and the neck that multiple incisions through the fascia above the episternal notch are necessary to release

2. Berry, F. B.: Wounds of the Thoracic Viscera, Am. J. Surg. **39**:12-17 (Jan.) 1938.

the air. Mediastinal compression is rather infrequent, inasmuch as active treatment was unnecessary in any case in this series and Stenbuck [3] reported that surgical intervention was necessary in only 2 cases in six years at Harlem Hospital.

*Hemothorax and Hemopneumothorax.*—In the series of cases of penetrating wounds, hemothorax or hemopneumothorax was present in 116 cases (77.2 per cent). Pure hemothorax was present in 55 (36.6 per cent). The amount of blood varied; in some cases it was just enough to obliterate the costophrenic angle, while in others it filled the entire pleural cavity. Hemopneumothorax was present in 61 (40.7 per cent) of the cases. In some of these hemothorax predominated, while in others there was only a small amount of blood but practically complete collapse of the lung. Most of the patients were treated conservatively. Therapeutic aspirations were done only for severe dyspnea and chest pain; diagnostic aspirations were done in most cases and repeated whenever the clinical course suggested the possibility of infection. In 56 cases of hemothorax and hemopneumothorax in which there were no other injuries or complications of any kind, the average hospitalization was thirteen and six-tenths days. These patients usually had fever for several days. In most of them the temperature rarely exceeded 101 F.; occasionally, however, temperatures of 103 F. or over were recorded. The average number of days in which the temperature reached 100 F. or over was six and nine tenths. It is of interest to note that 6 of these patients had extended periods of hospitalization of five weeks or more. These patients had elevations of temperature reaching 100 F. daily for twenty-four to thirty-six days. Repeated aspirations were sterile. Why these patients should have had such a protracted convalescence is a matter of conjecture.

Small simple hemothorax usually responds well when treated expectantly. This opinion is also held by Elkin,[4] Chandler and associates,[5] Harrington [6] and others. In cases of large simple hemothorax, aspiration and air replacement comprise the method of choice according to Foster and Prey [7] and Hegner [8]; in fact, these authors have recom-

3. Stenbuck, J. B.: Traumatic Subcutaneous Emphysema of Thoracic Origin, New York State J. Med. **37**:395-399 (Feb. 15) 1937.

4. Elkin, D. C.: Wounds of Thoracic Viscera, J. A. M. A. **107**:181-184 (July 18) 1936.

5. Chandler, F. G.; Mason, G. A.; Livingston, J. L.; Edwards, T., and others: A Discussion on the Treatment of Traumatic Hemothorax, Proc. Roy. Soc. Med. **34**:73-81 (Dec.) 1940.

6. Harrington, S. W.: Wounds of the Chest and Abdomen, Proc. Staff Meet., Mayo Clin. **15**:808-811 (Dec. 18) 1940.

7. Foster, J. M., Jr., and Prey, D.: The Treatment of Acute Traumatic Hemothorax, Ann. Surg. **100**:422-428 (Sept.) 1934.

8. Hegner, C. F.: Surgical Treatment of Injuries of the Chest, Am. J. Surg. **47**:394-407 (Feb.) 1940.

mended this form of treatment even for small hemothorax. Aspiration and air replacement is a simple procedure, practically devoid of danger after the initial forty-eight hours; it shortens the period of convalescence, and it is said by Foster and Prey to prevent the late complications of infection and deforming adhesions. In cases of persistent acute hemorrhage, aspiration and air replacement may be lifesaving; the treatment is universally recommended in the presence of severe dyspnea. In the series here reported, aspiration and air replacement were not used; the convalescence was not unduly prolonged in most cases, and the incidence of complications was small. Sandison and Elkin [9] have shown that blood and blood clots experimentally placed in the pleural cavity of dogs are rapidly absorbed and that their presence does not predispose to infection. Elkin utilized aspiration alone for pain and severe dyspnea in a group of 553 patients with penetrating wounds of the chest and reported a low incidence of septic complications. Allen [10] has suggested that hemothorax may well be treated by seepage with the wound in a dependent position for drainage. This method has also been successfully employed by Duff.[11] Autotransfusion of the blood aspirated from the pleural cavity has been recommended by Brown,[12] Butler [13] and Hegner.

For patients with extensive laceration of the lung in addition to hemothorax (a condition commonly seen in warfare), active therapy is certainly indicated. Aspiration and air replacement may be successfully utilized in some cases, but according to Chandler and associates, thoracotomy and repair of the lung will be required in many cases. In a small number of cases hemothorax arises from a severed intercostal or internal mammary artery. In these cases aspiration and air replacement are of no value; the bleeding vessel must be ligated, but frequently the pleural cavity need not be entered.

It seems reasonable to treat small to moderate hemothorax expectantly. Aspiration and air replacement should be used for large hemothorax and in the presence of respiratory embarrassment; open operation should be used when there is extensive lung laceration and when hemothorax is complicated by the presence of a large intrapleural foreign body. Bleeding intercostal and internal mammary vessels must

9. Sandison, J. C., and Elkin, D. C.: Penetrating Wounds of the Chest with Studies on Experimental Hemothorax, J. Thoracic Surg. **2**:453-467 (June) 1933.

10. Allen, D. S.: The Treatment of Penetrating Wounds of the Pleural Cavity, Arch. Surg. **21**:1161-1172 (Dec.) 1930.

11. Duff, P. H.: Penetrating Wounds of the Chest in Civil Life, Texas State J. Med. **29**:438-441 (Nov.) 1933.

12. Brown, A. L., and Debenham, M. W.: Autotransfusion: Use of Blood from Hemothorax, J. A. M. A. **96**:1223-1225 (April 11) 1931.

13. Butler, E.: Injuries of the Chest and Abdomen, Surg., Gynec. & Obst. **66**:448-453 (Feb.) 1938.

be ligated. Of course all treatment is countermanded until the initial shock is effectively combated.

*Pneumothorax.*—In cases of gunshot wounds in civil life pneumothorax alone is an infrequent finding. It was seen in only 3 (2 per cent) of the cases of penetrating wounds in our series. Open pneumothorax, caused by a sucking wound, must receive immediate attention to prevent mediastinal shift and severe respiratory embarrassment. The wound must be closed immediately, preferably by operative repair if the patient's condition warrants. An air-tight dressing may be employed in emergencies.

Ordinarily, pneumothorax prevents further hemorrhage and promotes healing by collapse of the lung; for this reason no immediate correction is indicated. Occasionally, a valvelike wound of the lung permits the entrance of air into the pleural cavity but prevents its exit. Constantly mounting pleural pressure results, and this positive pressure will interfere markedly with respirations and may demand immediate treatment. Usually aspiration of air is sufficient, but occasionally the aspirating needle must be connected to a tube under water to permit the periodic egress of the enclosed air with respiratory movement. In a few cases even this is insufficient, and operative repair is necessary. This is commonly called tension pneumothorax. There were no cases of this kind in this series.

## COMPLICATIONS

Of the complications, infection is by far the most important, excluding of course complicating injury to other organs.

*Infection.*—There were only 5 cases (3.3 per cent) in which there was infection of the wall of the chest in the series of cases of penetrating wounds. In addition to the single case of empyema following infection of the wall of the chest previously mentioned, there were 8 cases (5.3 per cent) of empyema. Four of the patients were admitted from other hospitals with already developed empyema. Empyema developed in our wards in only 4 (2.6 per cent) of the cases. In 1 of the remaining 4 patients, empyema developed after infection of a wound in the chest wall. In 2 patients with transection of the thoracic part of the spinal cord, empyema developed late in the course of the illness after several sterile aspirations. In the remaining case empyema was discovered at postmortem examination. Four of the 8 patients died. Cultures made in 4 of the cases revealed a different organism in each case; hemolytic streptococcus, staphylococcus, pneumococcus and Bacillus coli were present in 1 case each. In 1 patient, gangrene of one lobe of the lung developed; this lobe was removed, and the patient recovered. Empyema

was treated by rib resection and drainage in 3 cases and by closed drainage in 2. Two patients in desperate general condition were treated by repeated aspiration. No cases of lung abscess occurred.

Septic complications in these cases are infrequent in civil life. Elkin reported an incidence of empyema of 1.4 per cent in his series, while Boland [14] reported 1.7 per cent in his series. In wartime, however, empyema is much more common; Heuer and associates [15] found empyema in 17 per cent of their cases, while Bradford [16] reported an incidence of 25 per cent.

Infected hemothorax should first be treated by repeated aspiration. This was recommended by Chandler and associates for the purpose of localizing the infection and allowing time for the mediastinum to become stabilized. They stated that the principle emphasized in the treatment of empyema generally applies to this condition also, namely, that if rib resection is performed early, the resultant mediastinal shift will produce serious respiratory embarrassment and frequently contribute to death. Extensive pneumothorax also is present, and frequently the lung is unable to reexpand because of dense adhesions. Most surgeons agree that rib resection is the treatment of choice after the infection has become localized and the mediastinum fixed. A few surgeons, e. g., Bume and Liu,[17] have recommended aspiration and irrigation as long as the patient continues to improve on this regimen.

*Fractures.*—There were fractured ribs in 15 patients (10 per cent) with penetrating wounds. More than one rib was fractured in 5 patients (3.3 per cent); 1 had compound fractures. There were 7 patients with fractured vertebrae (4.6 per cent); 2 had fractured scapulas.

*Spinal Cord Injuries.*—Damage to the spinal cord was the only severe extrapulmonary complication in this series. There were 8 cases in which damage was present. Five of the patients died. Complete transection was observed in 7 cases; 1 patient had a Brown-Séquard type of hemisection. Laminectomy was done in 1 case.

## RESULTS

Twenty-six patients with penetrating wounds died—a total mortality rate of 17.3 per cent. Fifteen of these patients, admitted in a state of profound shock, died within twenty-four hours; the mortality rate after

14. Boland, F. K.: Traumatic Surgery of the Lungs and Pleura: Analysis of 1,009 Cases of Penetrating Wounds, Ann. Surg. **104**:572-578 (Oct.) 1936.

15. Heuer, G. J.; Pratt, G. P., and Mason, V. R.: Penetrating War Wounds of the Chest, Ann. Surg. **72**:352-369 (Sept.) 1920.

16. Bradford, J. R.: Gunshot Wounds of the Chest, Lancet **1**:227-232 (Jan. 29) 1916.

17. Bume, G. F., and Liu, W. L.: Gunshot Wounds of the Chest: Medico-Surgical Experiences During the Conflict in Shanghai, Chinese M. J. **47**:357-363 (April) 1933.

twenty-four hours was 7.3 per cent. Of the remaining 11 patients, 4 had transection of the thoracic spinal cord. If these are excluded, the mortality rate for thoracopulmonary wounds alone after the first twenty-four hours is 4.6 per cent.

### POSTMORTEM OBSERVATIONS

Reports of the coroner's postmortem examination were available in 18 cases. Deaths in the first twenty-four hours were uniformly due to

*Clinical Manifestations and Mortality Rates of Various Series of Cases of Penetrating Wounds of the Chest Reported in the Literature* *

| | | Clinical Manifestations | | | | | | Mortality Rates | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Authors | Cases | Subcutaneous Emphysema, per Cent | Pneumothorax, per Cent | Hemothorax, per Cent | Hemopneumothorax, per Cent | Hemoptysis, per Cent | Pleural Infection, per Cent | Total, per Cent | After Deducting Deaths Within First 24 Hr., per Cent | After Deducting Deaths Due to Other Visceral Injuries, per Cent |
| Connors, J. F., and Stenbuck, J. B.: Ann. Surg. **97**: 528-546 (April) 1933 | ... | 40 | 12 | .... | .... | .... | 6 | 12.6 | ... | ... |
| Elkin [4] | 553 | 40 | 24 | 37 | 36 | .... | 1.4 | .... | ... | 6 |
| Steinke, C. R.: J. Thoracic Surg. **8**: 658-665 (Aug.) 1939. | 87 | 25 | 18 | 36.7 | 11.5 | 43 | .... | 28.7 | ... | 11.6 |
| Boland [14] | 1,009 | 15 | 19 | 25 | 38 | .... | 1.7 | 13 | 9 | 8.5 |
| Stephens, H. W., and Cohn, S.: California & West. Med. **35**: 351-356 (Nov.) 1930 | 102 | .. | 29.5 | 71 | 24.5 | .... | 12.5 | 16.5 | 6.8 | 4.9 |
| Heuer, Pratt and Mason [15] | 160 | 11 (extensive) | 1.4 (pure) | 81 | 11 | .... | 17 | 26.6 | 13 | ... |
| Hardt and Seed | 150 | 40.7 (10, extensive) | 2 | 36.6 | 40.7 | 48.7 | 5.3 | 17.3 | 7.3 | 4.6 |

* Both knife and gunshot wounds are included in all series except those of Heuer, Pratt and Mason and of Hardt and Seed.

hemorrhage. Reports were available for 9 of the patients who died within twenty-four hours. One of these had large bilateral hemothorax, while 3 had large unilateral hemothorax. In 2 patients the parenchyma of the lung was extensively infiltrated with blood; 1 of these patients had small hemothorax in addition, while in the other the pleural cavities were obliterated by old adhesions. One patient had moderate hemothorax and huge bulging mediastinal hematoma. In 1 there was moderate hemothorax but with penetration of all three lobes of the right lung. The extent of the remaining patient's hemothorax was not

recorded. All 6 patients on whom no postmortem examination was performed died in profound shock.

Reports of the postmortem examination were available for 9 of 11 patients who lived longer than twenty-four hours. Two of these lived less than forty-eight hours, and hemothorax was present in both. In addition, 1 had old localized peritonitis (ulcerative enterotyphlitis Endamoeba histolytica). Four patients had lesions of the thoracic portion of the spinal cord. In addition, 1 had what is described as pyohemothorax; another, serofibrinous purulent pleuritis. One patient had perforation of both lungs with unilateral hemothorax. One patient had empyema; the lung of the remaining patient was densely infiltrated with blood. Of 2 patients for whom no autopsy was performed, 1 had pneumonia according to the clinical diagnosis. The second patient had empyema which had been drained; however, a brain abscess had developed.

## COMMENT

In the series of cases of penetrating wounds of the chest, the diagnosis of fractured ribs was made in only 10 per cent. This is probably a low figure since it is often difficult to be sure of this complication in a patient with superficial wounds and in shock. In many cases roentgen evidence is obscured by hemothorax. It is of interest that rib fracture was present in 50 per cent of the patients who came to postmortem examination.

According to Heuer, Pratt and Mason, the indications for early operation used by the American Medical Corps during the first World War were: (1) open sucking pneumothorax; (2) acute continuous hemorrhage; (3) large intrapleural or extrapleural foreign bodies, and (4) extensive rib fractures. To these the British author Gask [18] added: (5) ragged wounds of the soft parts; (6) persistent bleeding from the parietal wound; (7) compound rib fractures; (8) penetrating rib splinters; (9) tension pneumothorax, and (10) large clotted hemothorax. The German authors Landois [19] and Bumm [20] in articles covering the Polish and other campaigns mentioned approximately the same indications. Operations have been advised as soon as the patients recover from the initial shock. Careful review of the cases in our series in the light of these indications reveals few in which there were any

18. Gask, G. E.: Gunshot Wounds of the Chest, Brit. M. J. **1**:1043-1045 (May 20) 1939.

19. Landois, F.: The Evaluation and Therapy of Thoracic and Pulmonary Gunshot Wounds at Front, Med. Klin. **36**:449-452 (April 26) 1940.

20. Bumm, E.: Fundamentals of Treatment of Gunshot Wounds of the Thorax and Lungs: Experiences During the Polish Campaign, Med. Welt **14**:237-239 (March 9) 1940.

indications for early operation. Seventy-three per cent of the men operated on by Heuer and associates had large sucking open pneumothorax. In our series only 1 patient had this condition, and he died five hours after admission in profound shock. He had been given an air-tight dressing and shock treatment. Four of the patients mentioned by Heuer and associates had large intrapleural foreign bodies; 4 were operated on because of acute hemorrhage, and there was a question of injury in the abdominal cavity of 6 patients. Only among those with acute hemorrhage can we find any patients who might have been saved by early operation, and it is difficult in retrospect to be sure that an operation was needed even for them.

The early death of patients with penetrating wounds is almost exclusively due to hemorrhage. Bleeding may be intrapleural (hemothorax), or if the pleural cavity is obliterated or the wound in the lung sealed, blood may fill the parenchyma of the lung. Occasionally, bleeding from the large vessels in the mediastinum may produce large mediastinal hematoma and death. In deaths after forty-eight hours, lesions of the spinal cord and sepsis in the pleural cavity account for a large majority of the deaths.

## CONCLUSIONS

Thoracopulmonary gunshot wounds occurring in civil practice, if not rapidly fatal, are characterized by their slight tissue damage, low incidence of septic complications, early recovery and low mortality rate.

Hemorrhage is the common cause of early death. This may take the form of bleeding into the pleural cavity, bleeding into the parenchyma of the lung or bleeding into the mediastinum.

The common causes of late death are lesions of the thoracic portion of the spinal cord and sepsis.

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# GUNSHOT WOUNDS OF THE BRAIN

## REPORT OF TWO UNUSUAL COMPLICATIONS; BIFRONTAL PNEUMOCEPHALUS AND LOOSE BULLET IN THE LATERAL VENTRICLE

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Bullet wounds of the brain are by no means invariably fatal. If not killed outright by injury to vital centers or by massive hemorrhage and edema, many persons so wounded should recover. Their survival is made hazardous by hemorrhage, by necrosis and edema of the brain tissue and by infection. Even under the unfavorable conditions prevailing at the front during the last war, Cushing [1] was able to report a mortality rate of only 28.8 per cent [2] in a large series of cases.

In a small group of patients treated by us, two somewhat unusual complications were encountered. These were bilateral pneumocephalus and the presence of a loose bullet in the lateral ventricle. With military assignments in prospect for many, the records of these patients are of some interest.

### REPORT OF CASES

CASE 1.—*The patient had a gunshot wound of the brain with division of the left optic nerve. There were fractures of both frontal sinuses and the left cribriform plate. Bilateral pneumocephalus developed. Fascia lata repair of the dural lacerations were done and recovery followed.*

B. M., a 21 year old white man, was referred to Albany Hospital by Dr. L. W. Locke of Utica, N. Y., and Dr. Wardner D. Ayer of Syracuse, N. Y., on July 22, 1940. Twelve days previously, he had been accidentally shot at close range by a .22 caliber rifle. The bullet entered through the wall of the left orbit, where it fragmented. Its course through the apex of the orbit into the floor of the anterior fossa and in part through the the fractured frontal bone could subsequently be

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Read at the annual meeting of the Harvey Cushing Society, Rochester, N. Y., May 30, 1941.

1. Cushing, H.: Notes on Penetrating Wounds of the Brain, Brit. M. J. **1**:221, 1918; A Study of a Series of Wounds Involving the Brain and Its Enveloping Structures, Brit. J. Surg. **5**:20, 1918.

2. This figure does not include those patients who died before reaching the hospital.

traced in roentgenograms (fig. 1) from the position of the metallic particles. One piece could be both seen and felt beneath the skin of the right side of the forehead. The inner walls of the frontal and ethmoid sinuses were seen to be fractured. It was obvious from the direction taken by some bits of lead that both frontal poles of the brain had been injured.

At no time had the patient been unconscious or drowsy. While he had been immediately blinded in the left eye, vision in the right remained good. On one occasion only—the day following the injury—a bloody watery discharge from the nose had been observed. During the first week, he complained of left frontal and occipital headaches and at times of nausea and vomiting. There had been short periods of mental confusion. He had only slight fever and no paralysis or convulsions.

On admission to the hospital, twelve days after injury, the temperature and the pulse and respiration rates were normal. He was at times disoriented and inattentive. The wound of entry was apparently granulating satisfactorily. The left eye was proptosed by a large orbital hematoma and was blind and immobile. The left corneal reflex was absent, and sensation was diminished over the supra-

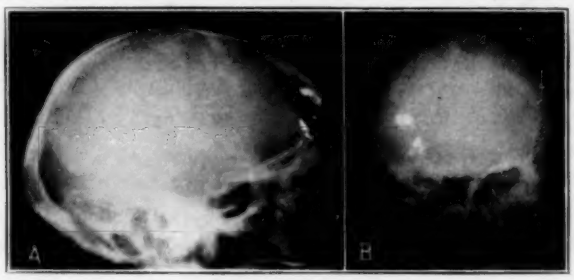

Fig. 1 (case 1).—*A*, lateral roentgenogram of the skull made two weeks after injury. The fragmentation of the lead bullet and the expanding fracture of the right frontal bone are evident. (Fracture lines extending through the frontal and ethmoid sinuses were clearly visible on stereoscopic examination.) *B*, the anteroposterior relation of the bullet tract to the frontal and ethmoid sinuses is shown. No intracranial air was present.

orbital and infraorbital areas on the left. Anosmia was present bilaterally. There was marked photophobia. The neck was rather stiff. Sustained ankle clonus could be elicited on each side. The remainder of the neurologic findings were normal.

*Laboratory Data.*—The blood count showed 10,600 white cells. Lumbar puncture revealed a pressure of 180 mm. of water. The cerebrospinal fluid was slightly xanthochromic and contained 19 polymorphonuclear leukocytes and 1 red blood cell per cubic millimeter. The total protein of the spinal fluid was 34 mg. per hundred cubic centimeters. The spinal fluid Wassermann test was negative.

Gradual improvement was observed until the twelfth day after admission, when a sore throat developed, and the temperature rose to 102 F. Although the stiffness of the neck had disappeared, the Kernig signs remained mildly positive. Elevation of temperature continued for the next week. During this time the leukocyte count in the blood was found to be normal, and the cell count in the spinal fluid was

never in excess of 6 white blood cells per cubic millimeter. On one occasion the pressure of the spinal fluid was 45 mm. of water, and on another it was practically atmospheric, although when the patient coughed it would rise to 100 mm.

During the next two weeks the patient again improved slowly, although at times he was confused and somewhat disoriented or, again, childish and emotionally unstable. During this time he began to complain of headaches in both the temporal and the occipital region. Not infrequently he became faint and vomited on sitting up. The spinal fluid pressure remained low (35 mm. of water), and the cell count revealed 10 lymphocytes per cubic millimeter.

Except on the day following the injury, rhinorrhea was not observed by the patient nor by any of his attendants until the following week—about a month and a half after the injury. He obeyed instructions not to blow his nose and so far as is known had not sneezed. Roentgenograms taken at that time showed bifrontal pneumocephalus (fig. 2). In retrospect, it seems likely that rhinorrhea had existed intermittently for some time and was responsible for the faintness, the nausea and

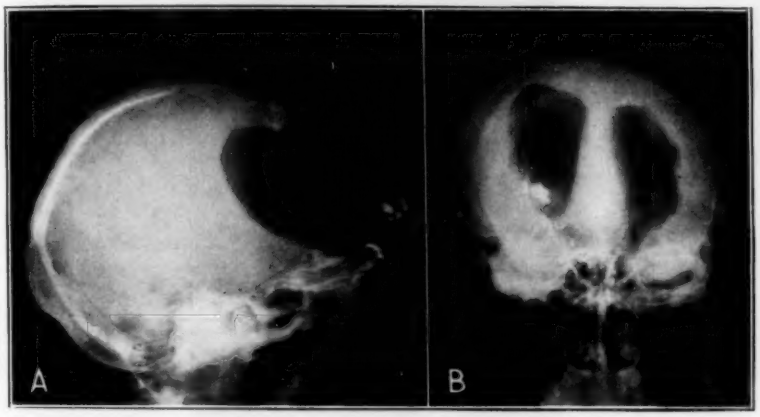


Fig. 2 (case 1).—*A*, lateral roentgenogram of the skull taken six weeks after the injury showing huge frontal pneumocephalus. *B*, posteroanterior roentgenogram showing bifrontal pneumocephalus. Note the fistulous openings in the frontal and ethmoid regions.

the headache which occurred on sitting up, and that it accounted also for the low spinal fluid pressures.

From a careful stereoscopic examination of the roentgenograms, fractures in the inner walls of the frontal and ethmoid sinuses on either side appeared capable of harboring fistulas. In any case, it was deemed necessary to explore both frontal fossae simultaneously.

*Operation.*—Operation was performed on Jan. 3, 1941. With the patient under anesthesia induced with ether and avertin with amylene hydrate, a coronal scalp incision was made, exposing both frontal bones. A small bone flap was then turned down on each side and hinged to the temporal muscle. There was no increase of intracranial pressure. The dura on the right side was adherent to the adjacent comminuted fracture, where the largest of the missiles had emerged. When the dura was opened, large, smooth, clean-looking cavities were found in

each frontal pole. These communicated through a bullet hole in the falx. Neither ventricle had been entered. Further inspection revealed fistulous openings through the shattered inner plates of both frontal sinuses and the left cribriform plate.

The dura was stripped from the base until the perforations were entirely in view externally, and then a large piece of fascia lata was snugly sutured in place on each side. Care was taken that the fascial patches overlapped the dura by at least 0.5 cm. everywhere, in the belief that this would facilitate the sealing-off process. The bone flaps were replaced, and the muscle, the galea and the skin were closed in layers with interrupted sutures of fine silk without drainage.

Convalescence was uneventful. The wounds healed by first intention. The patient's mind appeared to be clear, and he no longer acted in a childish manner. Save for blindness in the left eye and persistent anosmia, the neurologic abnormalities

Fig. 3 (case 1).—Photograph of the patient taken eight months after operation.

had entirely disappeared at the time of his discharge on January 29. Within two months he returned to work as a bank teller (fig. 3). At the time of writing, he has had no complaints for the past nine months.

Pneumocephalus [3] is a well known complication of cerebrospinal fluid fistulas which traverse the frontal, ethmoid, sphenoid or mastoid sinuses.[4] In civil life, fracture, tumor and infection are the more usual causes, although fistulas of "spontaneous" origin have been recorded. During

3. Dandy, W. E.: (*a*) Pneumocephalus, Arch. Surg. **12**:949 (May) 1926. (*b*) Pneumocephalus, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1, p. 311.

4. Woodhall, B., and Baker, T. W.: Pneumatocele Occipitalis, Arch. Surg. **42**:858 (May) 1941.

the last war, a number of cases were reported in which gunshot wounds were responsible. Any act which raises the intranasal air pressure, such as sneezing or blowing the nose, can force air through the fistula into the cranial cavity, where it may be trapped by the valvelike action of the adjacent meninges or the brain. The air may be located in the subdural or subarachnoid spaces, within the substance of the cerebrum or in the ventricles. Our patient was rather unusual in that he had two large air pockets, one in each frontal lobe, which communicated through an opening in the falx, and in that fistulous openings were present in both frontal sinuses and through the left cribriform plate. A fatal case of bilateral frontal pneumocephalus was reported by Lewis.[4a]

The symptoms of pneumocephalus are those of increased intracranial pressure and of the local destructive effects of an intermittently expanding air globule. While healing may take place spontaneously,[5] death occurs from intracranial pressure or infection in about half the cases in which treatment is not given.

Pneumocephalus is curable only by secure closure of the fistula; this has been pointed out by Dandy,[3] Cushing [6] and others.[7] Closure of the fistula can best be accomplished by suture or fascial repair of the dural laceration. If pneumocephalus is situated at the frontal [8] or mastoid [3a] sinuses, closure may be effected through a relatively small exposure, although in the majority of instances a low-placed osteoplastic bone flap is required. The approximate location of the opening can usually be determined by roentgen demonstration of a fracture through the sinus and of the corresponding location of the air. The latter is released at operation through a ventricular needle.

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4a. Lewis, A. J.: Traumatic Pneumocephalus, Brain **51**:221 (June) 1928.

5. Horrax, G.: Intracranial Aerocoele Following Fracture of Skull, Ann. Surg. **73**:18 (Jan.) 1921.

6. Cushing, H.: Experiences with Orbito-Ethmoidal Osteomata Having Intracranial Complications, with a Report of Four Cases, Surg., Gynec. & Obst. **44**: 721 (June) 1927; J. Am. S. A. **45**:1, 1927.

7. (*a*) Teachenor, F. R.: Intracranial Complications of Fistulae of Skull Involving Frontal Sinus, J. A. M. A. **88**:987 (March 26) 1927. (*b*) Munro, D.: The Modern Treatment of Craniocerebral Injuries, with Especial Reference to the Maximum Permissible Mortality and Morbidity, New England J. Med. **213**:893 (Nov. 7) 1935. (*c*) Cairns, H.: Injuries of the Frontal and Ethmoidal Sinuses with Special Reference to Cerebrospinal Rhinorrhea and Aerocoeles, J. Laryng. & Otol. **52**:589 (Sept.) 1937. (*d*) Coleman, C. C.: Fracture of the Skull Involving the Paranasal Sinuses and Mastoids, J. A. M. A. **109**:1613 (Nov. 13) 1937. (*e*) Campbell, E. H., and Gottschalk, R. B.: Osteoma of Frontal Sinus and Penetration of Lateral Ventricle, with Intermittent Pneumocephalus, ibid. **111**:239 (July 16) 1938.

8. Dandy.[3a] Teachenor.[7a]

If the opening lies in the cribriform plate, it may sometimes be seen through a nasal speculum, as in the case hereinafter cited. While healing has occasionally followed repeated local applications of a caustic,[9] such procedures have been condemned [10] since the results are uncertain and the patient may die from pressure or infection during the prolonged period usually required for treatment.

In the treatment of gunshot wounds of the brain, Cushing,[1] Horrax,[11] Van Wagenen [12] and others have shown that it is advisable to débride the entire wound—scalp, skull and brain—soon after the injury is received. When at all practicable, dural lacerations in the region of the air sinuses should be sought for and carefully closed at that time. It is probable that both local and general treatment with sulfanilamide or one of its derivatives will prove advantageous. Cerebrospinal fistulas through the frontal sinuses are readily accessible and may be repaired by simple suture of the dura or by fascial transplant.

Such a procedure was delayed in case 1, since the patient was apparently doing well when first seen two weeks after the injury, since the wound of entry was filled with none too clean-looking granulation tissue and since we found no evidence of pneumocephalus. In this particular instance, it is possible that had an operation been attempted immediately following the accident, the patient might not have tolerated bifrontal débridement and repair of dural defects in both anterior fossae. Earlier surgical intervention, however, would probably have prevented some of the loss of cerebral tissue caused by the enlarging pneumatoceles and would have shortened the stay in the hospital.

Dural lacerations over the cribriform plates are only slightly more difficult to handle. German [13] ingeniously used a flap of dura cut from the adjacent side of the crista galli. Adson [14] employed a bifrontal flap which permitted the simultaneous exposure of both sides of the cribriform plate. In addition to using the fascia lata in the case already reported,

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9. Fox, N.: Cure in a Case of Cerebrospinal Rhinorrhea, Arch. Otolaryng. **17**: 85 (Jan.) 1933.

10. Dandy.[3a] Coleman.[7d]

11. Horrax, G.: Observations on a Series of Gunshot Wounds of the Head, Brit. J. Surg. **7**:10, 1919; A Proposal for the More Radical Treatment of Gunshot Wounds of the Brain, Canad. M. A. J. **43**:320, 1940.

12. Van Wagenen, W. P.: Comment on Winslow, P.: Penetrating Wounds and Foreign Bodies of the Brain, Neurosurg. Ward Rounds **2** (nos. 3-4):1, 1941.

13. German, W. J.: Cerebrospinal Rhinorrhea—Operative Repair, Proc. Harvey Cushing Soc., 1941, vol. 10.

14. Adson, A. W.: Cerebrospinal Rhinorrhea: Surgical Repair of Craniosinus Fistula, Ann. Surg. **114**:697 (Oct.) 1941.

we have employed it in 1 other case. This second cribriform plate fistula occurred in a patient on whom a colleague performed submucous resection of the nasal septum. A gush of spinal fluid was observed when the septum was broken. By means of a nasal speculum, a large dural rent was readily visible through the left cribriform plate. Within an hour, the patient was anesthetized; a low frontal flap was turned down, and the dura was stripped from the floor of the anterior fossa until the tear was in plain view. Repair was then effected by means of a fascial transplant. Recovery was uneventful.

CASE 2.—*Gunshot wound of brain was complicated by a free bullet in the left lateral ventricle. The bullet was removed, and recovery ensued.*

E. W., a white woman 29 years of age, was referred to Albany Hospital on Aug. 29, 1940, by Dr. B. G. McKillip of Gloversville, N. Y. Three weeks previously, she had been accidentally struck in the left frontal region by a large lead buckshot, approximately through the coronal suture and 2 inches (5 cm.) from the sagittal suture. She was momentarily unconscious and for the next three days was nauseated and vomited. Fever was slight and of short duration. The neck was not stiff. No convulsions had occurred. Headache, which was maximal in the left temple, lasted for two weeks and then subsided. As she was right handed, there was some aphasia at first, which at the time of admission was gradually disappearing. A few days before admission, she suffered a brief attack of headache, nausea and vomiting. Tetanus antitoxin had been administered on the day of the injury.

On examination, she was seen to be alert, cooperative and in no distress. The wound was granulating, and a small bony defect was palpable beneath it. Speech had become normal, and no personality changes or memory defects were observed. There was mild weakness of the right side of the face and the right hand of the upper motor neuron type. The remainder of the neurologic findings were normal.

*Laboratory Data.*—Roentgenograms of the skull taken during the first week after the accident (fig. 4) disclosed the bullet lying deep within the left frontal lobe near the midline. A fragment of the missile lay just beneath the scalp near the point of entry. Roentgenograms taken two weeks later (fig. 5) showed, to our surprise, that the bullet was then located deep in the left occipital lobe. Since it appeared likely that it lay within the lateral ventricle, fluoroscopy was carried out. When the head was tilted, the bullet was observed to roll freely between the occipital and frontal regions and even part way down into the temporal horn. The patient experienced no abnormal sensation during these maneuvers.

Since she was afebrile and comfortable, it was decided that she should rest at home until the scalp wound was healed before removal of the bullet would be undertaken. Within a fortnight, however, she suffered a rather sudden severe headache, principally located in the left frontotemporal region and accompanied by projectile vomiting, photophobia, tinnitus and stiffness of the neck.

On readmission on September 12, the neurologic picture was unaltered, but for the first two days there was an evening rise of temperature to 100 F. (rectal) Slight cervical rigidity was present. The wound healed. There was no leukocytosis. Lumbar puncture revealed clear spinal fluid with an initial pressure of 48 mm. of water and a cell count of 210, approximately 65 per cent of which were poly-

morphonuclear leukocytes, the remainder being lymphocytes. The Pandy test was negative. On September 17, after she had been afebrile for three days, the spinal fluid pressure was found to be 110 mm. of water; the fluid was clear; the total protein content was 95 mg. per hundred cubic centimeters, and the cell count was 363, of which 78 per cent were polymorphonuclear leukocytes.

Reexamination by fluoroscopy at this time revealed the bullet lying in the occipital region and fixed. The visual fields were normal.

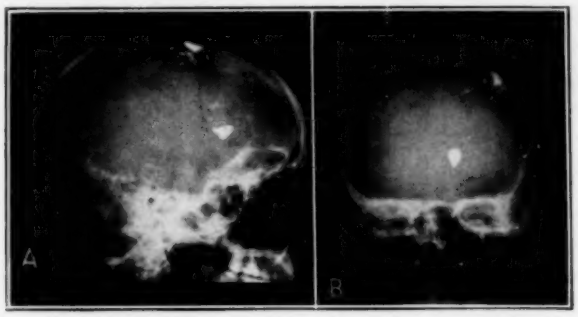


Fig. 4 (case 2).—Lateral (*A*) and posteroanterior (*B*) roentgenograms of the skull taken two weeks after injury. The bullet was located deep within the left frontal lobe, probably in the ventricle. A small fragment of lead remained beneath the scalp near the wound.

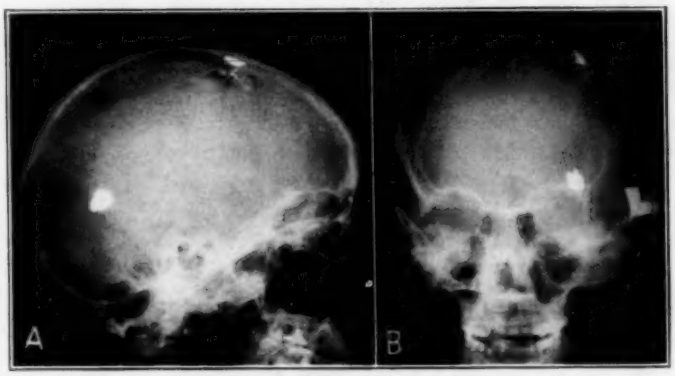


Fig. 5 (case 2).—Lateral (*A*) and anteroposterior (*B*) roentgenograms of the skull showing the bullet in the occipital horn of the left lateral ventricle. Under the fluoroscope the bullet could be observed to roll freely through the lateral ventricle.

*Operation.*—Operation was done on September 14. After the administration of 1,500 units of tetanus antitoxin on the previous day, a small osteoplastic bone flap was turned down in the left occipital region with the patient under anesthesia induced with ether and avertin with amylene hydrate. The dura and the cerebral cortex appeared normal in every respect. A short longitudinal incision was made into the posterosuperior portion of the lateral ventricle. A nasal speculum was

inserted. The bullet was not in sight. The body and the temporal horn of the ventricle appeared normal. The occipital horn was then inspected, and the bullet was found wedged within. It was removed without bleeding. The wound was closed in the usual manner with fine silk. On culture, the bullet (fig. 6) was sterile.

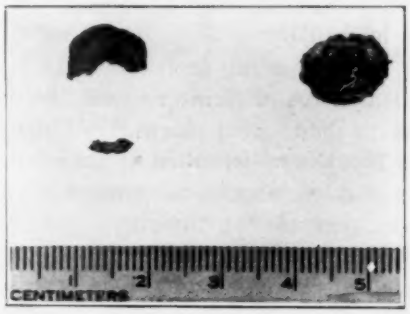


Fig. 6 (case 2).—Photograph of bullet fragments after their removal. The larger was removed from the ventricle.

Fig. 7 (case 2).—Photograph of the patient taken three months after operation.

Convalescence was uneventful. The visual fields remained normal. By the time of discharge, two weeks later, the weakness of the right side of the face and the right hand largely disappeared, as had also all evidence of aphasia. At a recent examination (fig. 7), some eleven months after operation, she was found to have no complaints; the neurologic examination gave entirely normal results, and she was doing her usual housework.

It has long been known that a bullet embedded in the brain may be or become sterile and thereafter be securely enclosed in scar tissue. Some may thus be harbored for years without producing any ill effects, while others may be held responsible for epileptic attacks, headache and vertigo, and their removal, along with as much of the associated cicatrix as possible, is thus indicated.

Foreign bodies in the lateral ventricles have been reported only occasionally. Probably most of them eventually become attached to the ependymal lining or to the choroid plexus.[15] While free, they may, or may not, produce symptoms by irritation or pressure. Our patient had bouts of headache, usually homolateral frontotemporoparietal, accompanied by mild fever, photophobia, tinnitus, slight cervical rigidity and pleocytosis of the spinal fluid. However, cultures of the spinal fluid and of the bullet on removal proved sterile. One of Dandy's patients was described as having such severe symptoms as to necessitate the bullet's removal. Kellhammer's [16] patient experienced no discomfort from a small round shot which wandered freely from the lateral ventricle to the lower part of the spinal canal. No notes are available on the case mentioned by Flesch-Thebesius,[17] and in Van Wagenen's patient, the symptoms were no doubt principally attributable to severe concomitant cerebral damage. From the small number of reported cases available, it appears likely that the majority of such foreign bodies in the lateral ventricles require removal.

## SUMMARY

An instance of bilateral frontal pneumocephalus and one of a loose bullet in the lateral ventricle, each following a gunshot wound of the brain, are reported. The methods by which these complications were satisfactorily dealt with are described.

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15. Dandy, W. E.: Cranial Injuries and Their Effect, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1, pp. 294-295.

16. Kellhammer, G.: Geschosswanderung in Ventrikelsystem, Zentralbl. f. Chir **66**:1773, 1939.

17. Flesch-Thebesius: Zentralbl. f. Chir., 1922, vol. 49, no. 24.

# THE HEPATIC (HEPATORENAL) FACTOR IN BURNS

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The whole truth about any series of burns is seldom if ever known, if for no other reason than that in the great majority of fatal cases the bodies, by law, must be turned over to the coroner, and detailed postmortem observations are therefore lacking. Related to this lack of pathologic knowledge is McClure's [1] charge that the average physician sees too few burns to know much about them; his estimate was that in ordinary practice he would see 1 burn in every four and one-half years and 1 fatal burn every twenty-three years. Elkinton,[2] finally, has commented on the surprisingly few studies in the literature on the constitutional aspects of burns, to which any one who has investigated hospital records might well reply that studies of these could scarcely appear in the literature since they are apparently not made on the patient.

A mere statement of mortality, furthermore, by no means tells the whole story of any series of burns. The mortality for the 1,243 burns treated at Charity Hospital of Louisiana at New Orleans in the six and one-half year period ending June 30, 1941 was 17.46 per cent (217 deaths). This is practically identical with the mortality of 17.6 per cent recently reported by McClure and Lam [3] from Henry Ford Hospital, Detroit. Both series included a large number of badly burned patients, but the facile statement that series in which high mortality is reported are likely to contain an undue proportion of badly burned patients, and vice versa, is not necessarily true.

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Read before the Piedmont Post-Graduate Clinical Assembly, Anderson, S. C., Sept. 9, 1941.

1. McClure, R. D.: The Treatment of the Patient with Severe Burns, J. A. M. A. **113**:1808-1812 (Nov. 11) 1939.

2. Elkinton, J. R.: The Systemic Disturbances in Severe Burns, and Their Treatment, Bull. Ayer Clin. Lab., Pennsylvania Hosp. **3**:278-291 (Dec.) 1939. Elkinton, J. R.; Wolff, W. A., and Lee, W. E.: Plasma Transfusion in the Treatment of the Fluid Shift in Severe Burns, Ann. Surg. **112**:150-157 (July) 1940.

3. McClure, R. D., and Lam, C. R.: Problems in the Treatment of Burns: Liver Necrosis as a Lethal Factor, South. Surgeon **9**:223-234 (April) 1940.

One of the paradoxes of burns is that it by no means follows that because a patient's burn is small he will inevitably recover. At Charity Hospital it was possible, by using Berkow's [4] table, to estimate the extent of body surface involved in 215 of the 217 fatal cases (fig. 1). Since a burn of 50 per cent of body surface ordinarily represents the upper limit of safety, death could reasonably have been anticipated in the 78 fatal cases in which this limit was exceeded. With equal reason, recovery might have been expected in a fair proportion, at least, of the 137 cases in which less than this area was involved. Certainly there was no reason to anticipate a fatal outcome in the 14 cases in which only 15

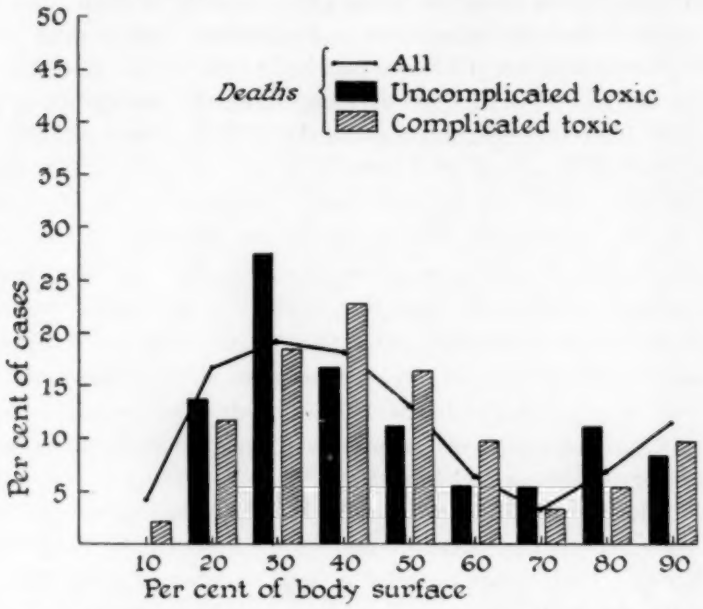


Fig. 1.—Distribution according to body surface involved of 215 fatal burns, 36 of which were associated with uncomplicated, and 92 with complicated, toxicity.

per cent and in the 9 cases in which only 10 per cent of the body surface was involved, or in many of the cases in which the burns were first and second degree (fig. 2). Such facts suggest that considerations other than the merely physical factors of extent and depth must enter into the matter.

An obvious factor is the patient's age, persons at the extremes of life being peculiarly susceptible to death from burns. More than a quarter of the 211 deaths at Charity Hospital in which the age of the

4. Berkow, S. G.: Value of Surface-Area Proportions in the Prognosis of Cutaneous Burns and Scalds, Am. J. Surg. **11**:315-317 (Feb.) 1931.

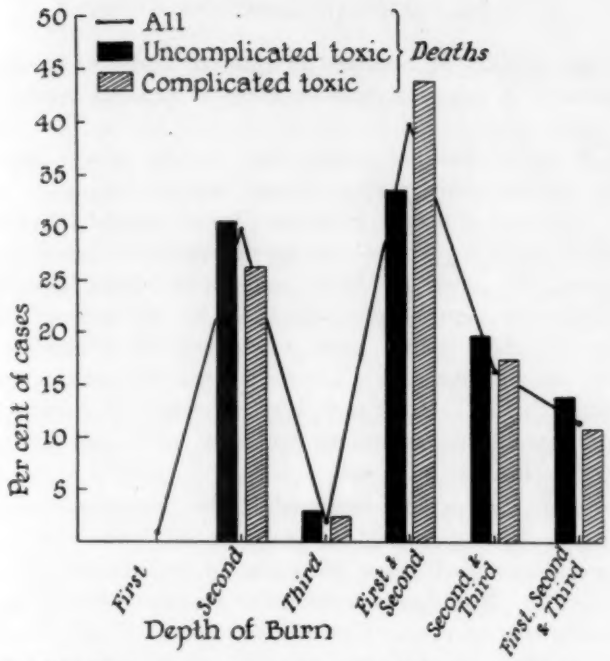


Fig. 2.—Distribution according to degree of 217 fatal burns, 36 of which were associated with uncomplicated, and 92 with complicated, toxicity.

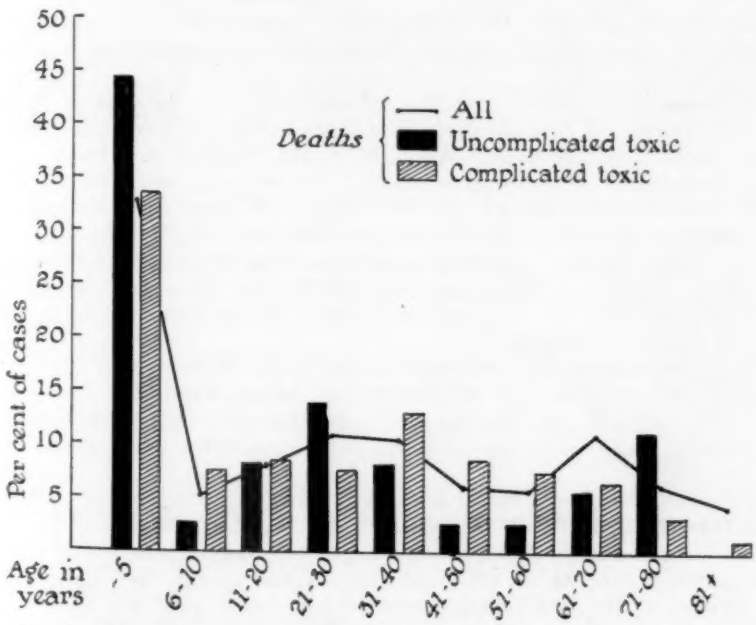


Fig. 3.—Distribution according to age of 211 fatal burns, 36 of which were associated with uncomplicated, and 90 with complicated, toxicity.

patient was known (fig. 3) occurred in children under 5 years of age, and approximately 20 per cent more occurred in patients over 70 years of age.

If there is any ground for complacency in the current belief that the mortality rate associated with burns has improved with the passage of years, the report of Dunbar [5] from the Glasgow Royal Infirmary, an institution which for fifty years has had special wards for burned patients, is well calculated to destroy it. In an analysis of 10,974 burns treated in the hundred year period ending in 1933, he pointed out that the mortality rate has never been as good in any year since 1868 as it was in many years prior to that date. The comment is the more devastating when one recalls that before that time, because of the incidence of sepsis, gangrene and tetanus in institutions, only the most severely burned patients were hospitalized.

Whatever improvement has occurred in the management of burns is undoubtedly to be traced to the concept of the burned patient as a person whose constitutional state is more serious, actually and potentially, than his local state. It is that concept which makes of special value the studies on burns carried out at Yale University,[6] at Henry Ford Hospital,[7] at the University of Pennsylvania [8] and at the University of Edinburgh.[9]

There is general agreement that all burns of any consequence exhibit certain distinct phases. There is equally general agreement concerning the first of these stages, shock, and the last two stages, the stage of

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5. Dunbar, J.: Review of the Burn Cases Treated in the Glasgow Royal Infirmary During the Past Hundred Years (1833-1933), with Some Observations on the Present-Day Treatment, Glasgow M. J. **134**:239-255 (Dec.) 1934.

6. Underhill, F. P.; Carrington, G. L.; Kapsinow, R., and Pack, G. T.: Blood Concentration Changes in Extensive Superficial Burns and Their Significance for Systemic Treatment, Arch. Int. Med. **32**:31-49 (July) 1923. Underhill, F. P.: Changes in Blood Concentration with Special Reference to the Treatment of Extensive Superficial Burns, Ann. Surg. **86**:840-849 (Dec.) 1927. Underhill, F. P., and Kapsinow, R.: The Alleged Toxin of Burned Skin, J. Lab. & Clin. Med. **16**:823-830 (May) 1931.

7. (*a*) Harkins, H. N.: Recent Advances in the Study of Burns, Surgery **3**:430-465 (March) 1938. (*b*) McClure.[1] (*c*) McClure and Lam.[3]

8. (*a*) Wolff, W. A.; Elkinton, J. R., and Rhoads, J. E.: Liver Damage and Dextrose Tolerance in Severe Burns, Ann. Surg. **112**:158-160 (July) 1940. (*b*) Footnote 2.

9. Wilson, W. C.: Extensive Burns and Scalds, Tr. Med.-Chir. Soc. Edinburgh **114**:177-192, 1934-1935; in Edinburgh M. J., October 1935. Wilson, W. C.; Jeffrey, J. S.; Roxburgh, A. N., and Stewart, C. P.: Toxin Formation in Burned Tissues, Brit. J. Surg. **24**:600-611 (Jan.) 1937. Wilson, W. C.; MacGregor, A. R., and Stewart, C. P.: The Clinical Course and Pathology of Burns and Scalds Under Modern Methods of Treatment, ibid. **25**:826-865 (April) 1938. Wilson, W. C.: Cause of Lethal Factors in Burns, Edinburgh M. J. **48**:85-93 (Feb.) 1941.

sepsis or infection and the stage of healing. Concerning the stage which follows shock, however, there is no agreement at all.

What this period is called depends chiefly on the point of view of the writer who is describing it. To use the term secondary shock for a stage ordinarily stated to last for several days seems something of a misnomer. To call it the stage of infection is equally incorrect. Aldrich's [10] theory that all findings during it can be explained by bacterial (streptococcic) infection has not been widely approved, and although he was able to culture the organism from the skin in all cases of severe burns and from the blood in all cases in which death occurred, his work has not been confirmed.

So much proof exists for both of the most important theories concerning this stage, the theory of hemoconcentration and the theory of toxemia, that it seems unwise to try to explain it as due exclusively to one pathologic process or to the other. That point of view seems justified even though the theory of hemoconcentration has been definitely established whereas much concerning the toxemic theory, including the isolation and identification of the hypothetic toxin, still remains to be proved.

Hemoconcentration as a possible factor in burns had been suggested as early as 1855, but it remained for Underhill, Kapsinow and their associates [6] to furnish the conclusive proof. There is now no dispute at all concerning (1) the dangerous diminution of blood volume in burns, due to loss of plasma from the blood and so-called white bleeding at the site of injury, and (2) the resulting hemoconcentration and increase in hematocrit values.

## THE TOXEMIC THEORY OF BURNS

Although the toxemic theory of burns has been discussed since 1876, no unanimity exists concerning it, and many observers probably still share Underhill and Kapsinow's point of view, that persistence in the acceptance of a burn toxin is an obstruction to the clarification of the problem.

It must be granted that much of the evidence is conflicting and contradictory. Avdakoff's statement [11] in 1876, to the effect that the blood of a burned animal is toxic to a healthy animal, was repeated, with and without proof, until 1923. In that year Robertson and Boyd,[12] in an extensive series of experiments, demonstrated that extracts of burned skin and the blood of burned animals produced toxic symptoms in intact

10. Aldrich, R. H.: The Role of Infection in Burns, New England J. Med. **208**:299-309 (Feb. 9) 1933.

11. Avdakoff, cited by Wilson and others.[9]

12. Robertson, B., and Boyd, G. L.: The Toxemia of Severe Superficial Burns, J. Lab. & Clin. Med. **9**:1-14 (Oct.) 1923.

animals and were sometimes lethal. Underhill and Kapsinow [6] could not confirm these results and expressed the opinion that any lethal factor which might be present was contained in the alcoholic content of the skin extracts.

Similar contradictory results followed Harrison and Blalock's [13] repetition of Vogt's [14] demonstration that the removal of burned skin prevented the development of toxemia in the injured animal and that its transplantation produced toxemic symptoms in the intact host. In their experiments the animals which were débrided actually died more rapidly than the untreated animals. Two years later Blalock [15] had apparently altered his views, for he made the statement that absorption of the extracts of burned tissue can cause shock and that deaths which occur from three to ten days after severe burns are in large part due to the absorption of products of protein degeneration.

Underhill and his associates [6] found no evidence of absorption from the burned area after the injection into it of such potent substances as strychnine or of such readily demonstrable substances as methylene blue. Mason and his associates,[16] however, after similar injections of potassium iodide, which is a readily diffusible substance of low molecular weight, found the rate of excretion in the urine to be almost identical in both burned and control animals.

The Japanese investigators are generally in favor of the toxic theory, but their experimental evidence, as Harkins [7a] has noted, is frequently open to criticism. In the same comprehensive and fair review of the subject, Harkins commented on the seventeen possible toxins listed by Fender [17] and proposed by thirty-four different investigators, but added that the mere multiplicity and confusion of ideas is no argument at all against the validity of the toxemic theory.

Rosenthal [18] found in the blood of human subjects and of certain burned animals a presumably toxic substance which caused contractions

13. Harrison, W. G., and Blalock, A.: A Study of the Cause of Death Following Burns, Ann. Surg. **96**:36-39 (July) 1932.

14. Vogt, E.: Versuche über die Uebertragbarkeit des Verbrennungsgiftes, Ztschr. f. exper. Path. u. Therap. **11**:191-222 (Oct.) 1912.

15. Blalock, A., in discussion on Heuer, G. J., and Andrus, W. DeW.: The Effect of Adrenal Cortical Extract in Controlling Shock Following the Injection of Aqueous Extracts of Closed Intestinal Loops, Ann. Surg. **100**:734-749 (Oct.) 1934.

16. Mason, E. C.; Paxton, P., and Shoemaker, H. A.: A Comparison of the Rate of Absorption from Normal and Burned Tissues, Ann. Int. Med. **9**:850-853 (Jan.) 1936.

17. Fender, F. A.: Lymphatic Pathology in Relation to the "Toxin" of Burns, Surg., Gynec. & Obst. **57**:612-620 (Nov.) 1933.

18. Rosenthal, S. R.: The Toxin of Burns, Ann. Surg. **106**:111-117 (July) 1937.

of the uterus of the virgin guinea pig, which was present both in red blood cells and in serum and which was not histamine, although it resembled histamine in some respects.

Wilson and his associates [9] carried out under strict aseptic precautions an ingeniously conceived and carefully controlled set of experiments with the edema fluid which accumulates at the site of burns. They produced such accumulations of fluid, without necrosis of the skin or injury to viscera, and later recovered the fluid and injected it into intact animals in various doses and at various intervals after the injury. For the first four hours this fluid, like the saline emulsions of normal skin, was harmless; thereafter it became progressively more toxic, and at forty-eight hours it was frequently lethal.

In this connection it is interesting to recall that Davidson's [19] tannic acid treatment, probably the most widely used local measure available today, was developed on the basis of a presumptive toxin in burns. Mason,[16] who made the suggestion to Davidson because he thought that deaths following burns, like death following the implantation of liver in the abdominal cavity,[20] might be due to tissue autolysis, believed that the absorption of toxins might be prevented by the use of tannic acid to precipitate the dead and dying tissues.

For a considerable period the contention of Underhill and his associates [6] that hemoconcentration adequately explains the second, so-called toxic stage of burns was accepted, if for no other reason than that no proof was produced by which it could be overthrown. Such proof has recently been brought forward by Lucido [21] and by Elkinton and his associates [8] in the form of detailed case studies by which it has been possible to show that a true stage of toxemia, in some instances terminating fatally, can occur when the hemoconcentration and plasma loss supposedly responsible for it can be demonstrated, by laboratory tests, to have been present and to have been entirely corrected.

If these observations can be corroborated in an adequate number of cases, they are of extreme importance, because they prove certain facts: (1) that clinical toxemia can exist in the absence of hemoconcentration and plasma loss; (2) that there is nothing essentially incompatible between the antecedent existence of hemoconcentration and the subsequent development of toxemia; (3) that there is no real reason why

19. Davidson, E. C.: Tannic Acid in the Treatment of Burns, Surg., Gynec. & Obst. **41**:202-221 (Aug.) 1925.

20. Mason, E. C.: A Note on the Use of Heparin in Blood Transfusion, J. Lab. & Clin. Med. **10**:203-206 (Nov.) 1924. Mason, E. C., and Nau, C. A.: The Causes of Death Due to Liver Autolysis, Surg., Gynec. & Obst. **60**:769-774 (April) 1935.

21. Lucido, J.: Metabolic and Blood Chemical Changes in a Severe Burn, Ann. Surg. **111**:640-644 (April) 1940.

toxemia and hemoconcentration should not exist simultaneously if hemoconcentration has not been corrected before toxemia sets in and if it is not at such a level (between 125 and 140 per cent) as to threaten life.

### THE HEPATIC FACTOR IN BURNS

A rather detailed discussion of the toxemic theory of burns is a necessary preliminary to the discussion of the hepatic or hepatorenal factor in burns. It would be an oversimplification of the subject to say that an acceptance of the toxic theory of burns presumes the existence of a liver or liver-kidney lesion or that the existence of these lesions always implies the presence of clinical toxemia. It is fair to say, however, that these clinical and pathologic findings are associated in a large number of cases and that the clinical picture of toxemia in burned subjects bears a striking resemblance to the clinical picture in such definitely hepatic states as the so-called liver death or liver-kidney syndrome.

The opponents of the toxemic theory of burns have been guilty of one curious omission. They have overlooked or otherwise failed to explain the hepatic lesion so frequently found in the postmortem examinations of burned patients. The omission is the more curious because Bardeen,[22] in what is generally granted to be the classic description of the pathologic process in burns, put particular emphasis on it. In his study of 5 fatal cases of burns, in all of which death occurred promptly after injury, he pointed out that the chief changes noted at autopsy were focal degenerations in the lymphatic tissues and the liver and advanced parenchymatous degeneration of the kidneys. He himself was so impressed with the similarity of the observations in the 5 cases that he said that a single description could easily suffice for them all.

How little attention has been paid to this phase of the subject is illustrated by its treatment in the comprehensive monograph on burns by Pack and Davis.[23] The liver is dismissed with the statement that the toxin of burns is cytotoxic for parenchymal organs and that the characteristic hepatic change consists of hyperemia, focal necrosis and parenchymatous degenerative lesions. The discussion of the pathologic changes in the kidneys, which have been considerably less universally ignored, is far more complete.

Scanty as is the postmortem evidence, there is no doubt that the liver lesion actually exists. It was present in some of the cases in the

22. Bardeen, C. R.: A Review of the Pathology of Superficial Burns, with a Contribution to Our Knowledge of the Pathological Changes in the Organs in Cases of Rapidly Fatal Burns, Johns Hopkins Hosp. Rep. **7**:137-179, 1899.

23. Pack, G. T., and Davis, A. G.: Burns: Types, Pathology and Management, Philadelphia, J. B. Lippincott Company, 1930.

Charity Hospital series in which postmortem examination was possible in the hospital laboratory, and it has been reported by McClure,[24] Elkinton,[8] Belt [25] and Zinck,[26] as well as by Wilson and his associates [9] in the most extensive and carefully recorded study of this type of burns.

The material studied by Wilson and his group consisted of 65 cases of serious burns, 23 of which were fatal and in 20 of which autopsy was permitted. To these 20 cases were added 13 others, in which less exhaustive studies had been made during life. In 14 of 16 cases in which clinical toxemia had been very severe, the liver had suffered intense damage, and milder degrees of damage could be correlated with less severe degrees of toxemia in a smaller number of cases.

Experimental studies also serve to corroborate the existence of a liver or a liver-kidney lesion in burns. As early as 1904 Parascandolo [27] had described fatty degeneration of the liver and the kidneys, presumably caused by a circulating toxin with a specific effect on these organs. The changes found by Robertson and Boyd [12] after the injection of extracts of burned skin and of blood from burned animals included cloudy swelling, fatty metamorphosis and parenchymatous degeneration of the liver and cloudy swelling of the kidneys.

In the experimental studies of edema fluid collected from the burned area carried out by Wilson and his associates,[9] the liver was invariably the organ which had sustained the greatest damage, and the changes were invariably degenerative and necrotic in character. These authors expressed the belief that such changes, either clinically or experimentally, could not be produced by any agent other than a powerful toxin with an apparently specific action on the liver.

## THE CLINICAL PICTURE OF TOXEMIA

The clinical picture of the so-called toxemia of burns is generally agreed on, even by those who decline to describe the syndrome as toxic. Symptoms may appear as early as six or eight hours after injury, though they more often occur between the third and fifth days or sometimes later. Shock is not necessarily an antecedent. The onset is usually insidious, and the syndrome often develops in a patient whose progress has been satisfactory or even good, and who has certainly given no cause for anxiety. For some inexplicable reason the toxemic state is rather more likely to be associated, particularly in its fatal form, with super-

24. McClure.[1] McClure and Lam.[3]

25. Belt, T. H.: Liver Necrosis Following Burns, Simulating the Lesions of Yellow Fever, J. Path. & Bact. **48**:493-498 (May) 1939.

26. Zinck, K. H.: Gestaltliche Leber-Nierenschädigungen und hepato-renale Insuffizienz nach Verbrennung: Ein Beitrag zur Frage des Verbrennungskollapses, Klin. Wchnschr. **19**:78-84 (Jan. 27) 1940.

27. Parascandolo, cited by Harkins.[7a]

ficial and limited rather than with extensive burns (figs. 1 and 2). The Charity Hospital statistics are not unusual in this respect.

A change in the mental state is one of the first symptoms. The patient may become restless, irritable and apprehensive in turn. He is first drowsy and then comatose, or he may pass from disorientation into delirium, which may be extreme and which is always a bad sign, particularly if it comes on early. Convulsions are frequent in young children. The fever mounts rapidly, the temperature reaching 105 F. or higher, and the pulse and the respiration are correspondingly rapid, though the respiration is not otherwise altered. Vomiting is usually present. The skin and mucous membranes have a cyanotic or grayish tinge, the eyes are sunken and the pupils are dilated. In the fatal cases death is seldom long deferred.

The most obvious manifestation of the hepatic lesion is the development of jaundice. Pack and Davis [23] did not mention it as a possible complication of burns, but it was present in a number of cases in the Charity Hospital series and has been reported by McClure,[1] McClure and Lam,[3] Zinck [26] and others who have paid special attention to this phase of burns.

Wilson and his associates [9] regard jaundice not as a complication of burns but as an integral part of the pathologic process. It was present in 12 of the 65 cases of serious burns which they studied, and they observed, significantly, that the incidence would have been higher had they realized its significance and looked for it earlier in their study. It was not related to the presence of sepsis or to the mode of treatment but seemed a definite index of the degenerative and necrotic changes observed in the liver in the fatal cases in which autopsy was permitted.

Children and adolescents are peculiarly susceptible to this complication, and it is peculiarly fatal in these age groups (fig. 3). Wakeley [28] commented on the unusually low incidence of toxemia in the soldiers and sailors rescued from Dunkirk and on their excellent toleration of this stage, when it did develop, even though treatment was delayed and conditions were often unfavorable for recovery. He attributed this toleration to their good physical condition. There is another possible explanation, however, of the low incidence of toxemia and its low mortality in this particular group of patients. It is implicit in Wakeley's later statement [29] that in his opinion infection was the most frequent cause of toxemia in the more than 1,000 *war* (italics mine) burns which he treated. In other words, Wakeley was discussing bacterial toxemia and not the hepatic

28. Wakeley, C. P. G.: War Burns and Their Treatment, Practitioner **146**: 27-37 (Jan.) 1941.

29. Wakeley, C. P. G.: The Treatment of War Burns, Surgery **10**:207-232 (Aug.) 1941.

type of toxemia with which this paper is concerned, the incidence of which, as will be pointed out later, is never large, though the mortality is always high.

## THE LABORATORY ASPECT OF THE HEPATIC FACTOR IN BURNS

It is not possible by any tests so far available to predict the development of toxemia in any given case, which is unfortunate, for once toxemia has fully developed, it is almost impossible to combat it. On the other hand, laboratory tests of hepatic function have supplied further evidence of the role of the liver in the toxemia of burns.

An elevated icteric index would, of course, be expected in the presence of jaundice, clinical or latent. The warning might profitably be issued, however, that jaundice does not always indicate hepatic damage; in some instances it may be of the hemolytic variety.

My own studies with the Quick hippuric acid test of liver function in burns, supplemented in a few cases with the serum bilirubin test, have been reported in detail elsewhere.[30] They are not numerous, but in practically every instance some degree of functional impairment was found, which was frequently, though not constantly, capable of rough correlation with the surface area and the depth of the lesion. These observations are in accord with those of others [31] who have made such studies.

The carefully controlled cases reported by Wolff, Elkinton and Rhoads [8] offer valuable corroborative evidence of the liver factor in burns. The disturbances of fluid balance were shown by laboratory evidence to have been corrected within forty-eight hours of the injury, yet the serum bilirubin, bromsulphalein, hippuric acid, plasma prothrombin and dextrose tolerance tests, all of which were carried out one or more times, showed at some time deviations from normal. In view of the number and variety of tests, the liver damage thus indicated can reasonably be accepted at its face value.

In a personal case, reported in detail elsewhere,[30] the initial value for the hippuric acid test was only 29.3 per cent of normal, though the burns were only of second degree and involved only 25 per cent of the body surface. Convalescence, although slow, was reasonably satisfactory, but only on one occasion did the serial tests of liver function by the Quick method rise above 60 per cent of normal. On the twenty-eighth day mesenteric thrombosis developed, for which extensive resection of the small bowel was done without undue delay or special difficulty. After a period of remarkably gratifying improvement the patient began

30. Boyce, F. F.: The Rôle of the Liver in Surgery, Springfield, Ill., Charles C. Thomas, Publisher, 1941.

31. McClure.[1] McClure and Lam.[3] Zinck.[26]

to do badly, and death occurred on the tenth postoperative day (the thirty-eighth day after the injury). The localized peritonitis found at autopsy was perhaps sufficient to explain the death, but not to be ignored were the marked degenerative changes found in the liver, which were in keeping with the constantly depressed hepatic function. The case is to be compared with the case reported by Wilson and his associates,[9] in which postmortem examination of a patient who died of accidental causes fourteen days after a burn revealed intense necrotic changes in the liver.

### PATHOLOGIC ASPECTS OF THE LIVER LESION

Wilson and his associates [9] have provided the most detailed description of the liver lesion in burns. It was not present in any of their cases in which death occurred earlier than twenty-one hours after injury, though I have personally observed it as early as eight hours (fig. 4). From twenty-one to fifty-seven hours, the characteristic change, which was discernible only by the microscope, consisted of fatty metamorphosis of the epithelial cells surrounding the efferent veins in the central zone of the hepatic lobules, accompanied by nuclear damage, especially karyolysis.

From fifty-seven hours onward, gross changes were evident to the naked eye. The liver was slightly enlarged, light yellow, soft, greasy and friable. On section, the central zone, although usually pallid, was sometimes hemorrhagic, and the liver was of the nutmeg variety. Microscopic study, in the light of microscopic studies in earlier fatal cases, made it clear that the underlying pathologic process was essentially a degeneration leading to necrosis of the parenchymal cells. Definite signs of severe bacterial infection were observed in 8 of 13 cases in which death was deferred, sometimes as long as six weeks after injury, but typical liver lesions were found in the remaining cases.

In the extent and completeness of destruction of hepatic tissue, Wilson and his associates pointed out, the microscopic picture was comparable with that of acute yellow atrophy of the liver, differing only in the constant, characteristic zonal distribution. In their opinion, "the liver lesion furnished the strongest indication of a non-bacterial toxin circulating during the first few days after a burn." They added that in the extensive studies which they carried out they were never able to associate the development of toxemia with hemoconcentration per se, with the growth of any type of organism in the burned area, with the changes in blood chemistry frequently though not constantly present in burns or with any other cause except the liver lesion described. Elkinton [2] also made the point that the liver lesion of burns is not associated with the acute visceral congestion and hemorrhage typically present in patients dying of hemoconcentration.

Wilson and his associates pointed out that the hepatic lesion of burns differs from a lesion of bacterial origin in that the central rather than the peripheral zone is affected and that the liver cell injury is far more pronounced.

Fig. 4.—Photomicrograph (× 192.3) of the liver showing hyperemia, cloudy swelling and slight lymphocytic infiltration of periportal tissue in a case of third degree burns in which death occurred in seven hours.

In 4 of the 5 cases studied in detail by Buis and Hartman [32] the postmortem observations were similar to those described by Wilson and his associates. Midzonal necrosis was also a characteristic feature in the

32. Buis, I. J., and Hartman, F. W.: Histopathology of the Liver Following Superficial Burns, Am. J. Clin. Path. **11**:275-287 (April) 1941.

4 cases studied intensively by Belt,[25] who pointed out the similarity of the hepatic lesion in burns and in yellow fever.

On the other hand, extreme changes are by no means always the rule, nor is necrosis the only type of hepatic lesion found. Eppinger [33] mentioned serous inflammation of the liver, and Keschner and Klemperer [34] commented on the relatively high incidence of hepatic edema in burns. In many instances cloudy swelling (fig. 4) or fatty metamorphosis (fig. 5) is the chief hepatic change.

Zinck [26] attributed the lobular necrosis of the liver observed in many of his own cases to the state of the capillaries, which in turn he attributed to the action of protein degradation products from the burned area. This explanation, in one form or another, underlies the whole theory of the toxemia of burns, though certain other causes may also play a part.

It is quite possible that anoxia is responsible for part of the picture. It is one of the phases of the stage of hemoconcentration, and lack of oxygen has been clearly shown by Hawkins,[35] Judd, Snell and Hoerner [36] and Ravdin and his associates [37] to have a distinctly adverse effect on the liver.

Fatty metamorphosis is open to two possible explanations. It may be the result of hyperglycemia, which is part of the first stage of burns and which is associated with a prompt loss of glycogen from the liver and other tissues. It may also be due to the protein loss associated with plasma loss. As Ravdin [38] has demonstrated, protein deficiency leads to an excessively high lipid content in the liver.

Pierre Duval,[39] who believes that autolyzing tissue at the site of the burn acts as a toxin, has suggested that repeated burns may so sensitize an animal as ultimately to confer a certain immunity or resistance to this type of injury. In the same connection, Wilson and his associates [9] have suggested anaphylaxis as a possible explanation of the occasional

33. Eppinger, cited by Zinck.[26]

34. Keschner, H. W., and Klemperer, P.: The Frequency and Significance of Hepatic Edema, Arch. Path. **22**:583-592 (Nov.) 1936.

35. Hawkins, J. A.: Acceleration of Blood Coagulation by Breathing Oxygen, Proc. Soc. Exper. Biol. & Med. **31**:1095 (June) 1934.

36. Judd, E. S.; Snell, A. M., and Hoerner, M. T.: Transfusion for Jaundiced Patients, J. A. M. A. **105**:1653-1658 (Nov. 23) 1935.

37. Goldschmidt, S.; Ravdin, I. S., and Lucké, B.: Anesthesia and Liver Damage: I. The Protective Action of Oxygen Against the Necrotizing Effect of Certain Anesthetics on the Liver, J. Pharmacol. & Exper. Therap. **59**:1-14 (Jan.) 1937. Ravdin, I. S.; Vars, H. M.; Goldschmidt, S., and Klingensmith, L. E.: Anesthesia and Liver Damage: II. The Effect of Anesthesia on Blood Sugar, the Liver Glycogen, and Liver Fat, ibid. **64**:111-129 (Sept.) 1938.

38. Ravdin, I. S.: Some Recent Advances in Surgical Therapeusis, Ann. Surg. **109**:321-333 (March) 1939.

39. Duval, P,. cited by Rudler, J.: Etat actuel du traitement des brûlures superficielles en pratique courante, Bull. méd., Paris **49**:343-347 (May 18) 1935.

deaths which occur promptly after burns not of sufficient severity to account for the fatality. In support of their argument they cited the case of a patient who had sustained a burn a year prior to the second burn, from which he died in twenty-four hours, though it involved only 5 per cent of the body surface.

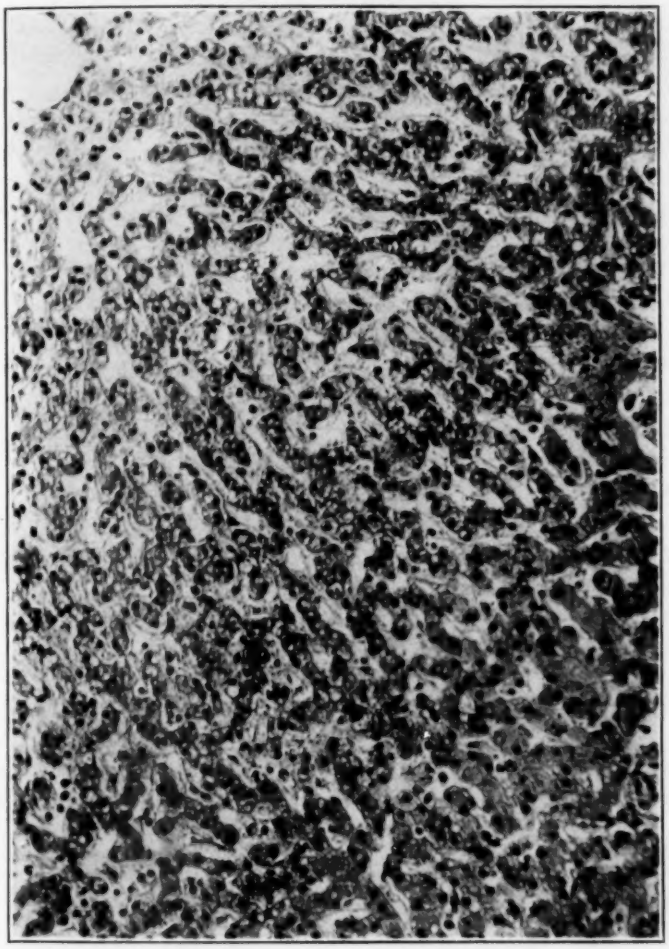

Fig. 5.—Photomicrograph (× 192.3) of the liver showing marked fatty metamorphosis in a case of first and second degree burns, in which the liver-kidney type of death occurred in five days. Compare with the kidney shown in figure 6.

When tests of liver function are employed to demonstrate a possible hepatic factor in burns, it must not be forgotten, particularly in older patients, that a demonstrable depression may possibly be due, at least in part, to preexistent hepatic damage. I have set forth elsewhere [30] my own view and the views of others on the "liver weakling," and the

theory really strengthens the case for the liver factor in burns, since a subject whose liver is already damaged would seem peculiarly liable to the prompt development of additional hepatic damage.

### THE RENAL (HEPATORENAL) FACTOR IN BURNS

That the renal lesion in burns should have been recognized for many years is not surprising, since albuminuria and hematuria are rather frequent findings, and oliguria and even anuria are not really uncommon. Changes in the chemistry of the blood may include large increases in nonprotein nitrogen and slighter increases in the urea. It is difficult to evaluate the so-called residual nitrogen, on which Zinck [26] and other German investigators lay such stress, since it is not usually determined in American laboratories.

These findings are usually explained either as the direct result of the burn on the kidney or as due to a diminution in the ability of the kidneys to excrete toxic degradation products because of loss of chlorides into the tissues, both from the burned area and as the result of vomiting. Both of these explanations are probably correct. They do not, however, cover such cases as have been reported by Lucido [21] and by Zinck [26] or as I myself have observed,[30] in which uremic manifestations are present without any laboratory evidence of renal insufficiency.

Cases of this type can readily be explained by the concept that uremic manifestations and alterations in kidney function and blood chemistry are not always an index of renal insufficiency per se but are rather a reflection of liver damage and of its effect on the kidney. This theory is in accord with the suggestion of Wilensky and Colp [40] in 1927, that chemical tests of renal function are useful as indexes of liver function. Elsewhere [30] I have cited both clinical and experimental evidence to show that efficient kidney function is at least partially dependent on and maintained by efficient liver function. Nonnenbruch [41] suggested that liver damage may be so great in some cases as to result in complete failure of the function of urea formation.

This explanation of the renal factor in burns leads directly to the parallel between this type of injury and the so-called liver death and liver-kidney syndrome. Deaths which occur promptly after burns, with hyperpyrexia and hepatic necrosis as the outstanding features, correspond to the so-called liver death. Deferred deaths, in which the renal factor is outstanding and postmortem examination reveals pathologic changes

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40. Wilensky, A., and Colp, R.: Relation of Nitrogen Bodies of the Blood to Surgical Problems in Liver and Biliary Tract Disease: III. Status of Nitrogen Bodies of Blood in Severe Cases of Biliary Tract Disease and Its Use in Differentiating a Terminal Hepatic and a Terminal Renal Group of Cases, Arch. Surg. **15**:635-659 (Oct.) 1927.

41. Nonnenbruch, cited by Zinck.[26]

in both the liver (fig. 5) and the convoluted tubules of the kidney (fig. 6), correspond to the so-called liver-kidney syndrome.

The parallel is both clinical and pathologic. It therefore does not seem unreasonable to explain certain deaths after burns on the same basis as so-called liver or liver-kidney deaths. Briefly, the liver finally

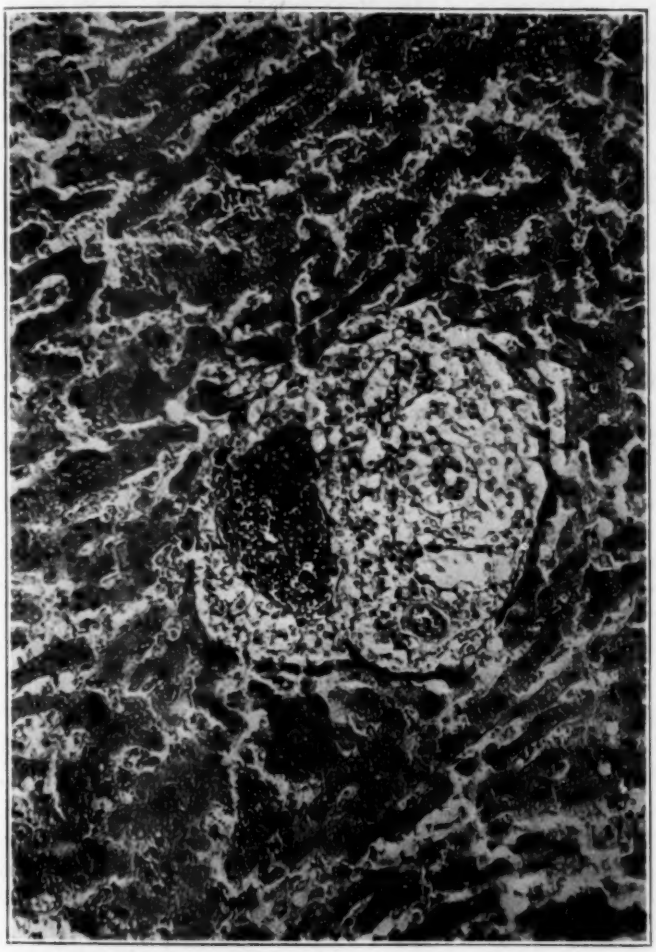

Fig. 6.—Photomicrograph of a kidney showing marked degenerative changes in the tubular epithelium and intraglomerular hemorrhage in a case of first and second degree burns, in which the liver-kidney type of death occurred in five days. Compare with the liver shown in figure 5.

fails in its function of detoxification because it is completely overwhelmed by the toxins poured out into the circulation from the burned surface. If the patient lives long enough, the kidney is overwhelmed in its turn. It is the second great organ of detoxification in the body, and when liver

function fails it takes on a hyperfunction utterly beyond its ability to carry on for any sustained period.

### THE INCIDENCE OF TOXEMIA IN BURNS

It should not be assumed, from what has been said, that well marked toxemia is an inevitable or even an especially frequent development in the usual run of unselected burned patients. The series reported by Wilson and his associates [9] is not in the least typical. It consisted of cases selected frankly because the condition was serious or was likely to be.

A careful analysis of the 1,243 burns treated at Charity Hospital in the period specified is proof of the relative infrequency of toxemia of

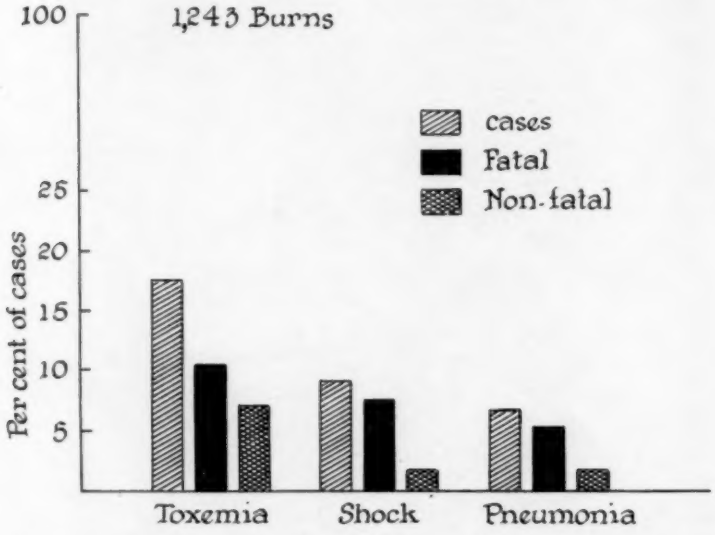


Fig. 7.—Distribution of certain complications and causes of death in 1,243 burns, 217 of which were fatal. The figures for the various groups are overlapping.

any degree both in fatal and in nonfatal cases (fig. 7). Toxemia of all degrees played a part in more cases than either shock or pneumonia, but toxemia of extreme degree was relatively infrequent; this is shown by the number of fatal cases in which, either alone or in combination, it played any part (fig. 1). It is doubtful whether it would play a greater average role in any other unselected series of burns of all degrees of extent and depth.

### THERAPEUTIC CONSIDERATIONS RELATED TO THE HEPATIC FACTOR IN BURNS

Although a discussion of therapy forms no part of a paper such as this, certain general principles of treatment are related to the phase of the subject under discussion. An institution which undertakes the

treatment of so serious a condition as burns should have a definite therapeutic regimen, no detail of which should be left to chance and which should have as its point of departure the concept that the patient's general condition is more important than his local condition.

From the standpoint of the hepatic or toxemic factor, however, local measures are not unimportant. Advocates of the toxemic theory are in rather general agreement that acute toxemia can be minimized by adequate local measures, including the use of a tanning agent. Even Dunbar,[5] who cannot bring himself to believe that toxemia is due to absorption from breaking down proteins, has granted that if the traumatized area is kept sterile this clinical stage is less likely to develop.

The restoration of the disordered fluid balance is not directly related to the liver factor except that the administration of plasma is helpful in respect to the liver, in view of Ravdin's [38] demonstration that fatty metamorphosis is decreased or prevented by the use of a high protein intake. Plasma should be administered on a strictly calculated basis, both as to the amount needed and as to the period of administration. The formula proposed by Harkins [42] for this purpose, because of its simplicity, is generally applicable.

Administration of dextrose must be carried out if the theory of hepatic damage is accepted, but the promiscuous giving of fluids is never warranted. If dextrose can be given by mouth, the risk of excessive fluid administration is avoided. Althausen [43] has demonstrated the effectiveness of the oral route, and my own studies [30] with the Quick hippuric acid test of liver function corroborate his evidence. Seriously ill patients, however, who need carbohydrates most of all, are likely to be vomiting, and dextrose must be given by infusions; these should be given very slowly and on the basis of the patient's calculated needs.

Certain other therapeutic measures should be reevaluated in the light of their possible effect on the liver. Thus Elman's [44] suggestion that in an emergency, while plasma is being secured and prepared, a single administration of gum acacia is useful, since this agent has proved colloidal properties, is accompanied by the warning that its deleterious effects on the liver also have been proved.

Anesthesia for preliminary débridement and cleansing should be avoided whenever possible, not only because it is undesirable in a shocked subject, but in view of my own demonstration,[30] which confirms the

42. Harkins, H. N.: The Treatment of Burns with Particular Emphasis on the Management of Burn Shock, Brochure prepared in connection with Exhibit on Burn Shock, Meeting of American Medical Association, Cleveland, June 2-6, 1941.

43. Althausen, T. L.: Dextrose Therapy in Diseases of the Liver, J. A. M. A. **100**:1163-1167 (April 15) 1933.

44. Elman, R.: The Therapeutic Significance of Plasma Protein Replacement in Severe Burns, J. A. M. A. **116**:213-216 (Jan. 18) 1941.

work of others,[45] that a depression of liver function accompanies any type of anesthesia, even in normal subjects. A patient given proper sedation can usually be treated without anesthesia.

Finally, sulfanilamide and its derivatives, which have been used for some time in infected burns and the wider use of which is now being advocated, should be employed with caution. My own evidence[30] corroborates the evidence of others[46] that these drugs may have a damaging effect on the liver, and these effects are likely to be enhanced if the drugs are used without due precautions for patients whose livers are already damaged by the toxins of burns.

## SUMMARY AND CONCLUSIONS

Although the universal application of the theory of hemoconcentration in burns is granted, it is pointed out that considerable valid evidence also exists in favor of the toxemic theory, and it is suggested that the two theories are not mutually exclusive.

The hepatic factor in the nonbacterial toxemia of burns is discussed from the experimental, clinical, laboratory and pathologic (postmortem) aspects.

The renal lesion in burns is considered as a secondary phase of the hepatic lesion, and a parallel is traced between certain deaths from burns and the so-called liver death and liver-kidney syndrome.

It is pointed out that well marked toxemia plays a part in only a small proportion of burns, whether fatal or nonfatal.

The therapy of burns is discussed in its relation to the liver factor.

A certain mortality is probably inevitable with burns. Generally speaking, persons who are burned extensively are unlikely to recover, regardless of the method of treatment employed, while at the other extreme patients who are slightly burned are likely to recover, though certain entirely unexpected deaths may occur in this group. The patients who provide these unexpected fatalities and the patients in the middle group, who may or may not recover and whose chances of life are chiefly dependent on how they are treated, offer the greatest opportunities for improvement in the present unhappy mortality from burns.

Attention to the hepatic and hepatorenal aspects of this type of injury is therefore suggested as one possible method of achieving this improvement.

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45. Bourne, W.: Anesthetics and Liver Function, Am. J. Surg. **34**:486-495 (Dec.) 1936. Coleman, F. P.: The Effect of Anesthesia on Hepatic Function, Surgery **3**:87-99 (Jan.) 1938.

46. Watson, C. J., and Spink, W. W.: Effect of Sulfanilamide and Sulfapyridine on Hemoglobin Metabolism and Hepatic Function, Arch. Int. Med. **65**:825-846 (April) 1940.

# SULFATHIAZOLE OINTMENT IN THE TREATMENT OF BURNS

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The treatment of burns in war injuries has brought out important points not hitherto well recognized. First, it has been found that the tannic acid treatment is not so satisfactory as is commonly stated.[1] Second, the life-saving value of plasma replacement has been satisfactorily demonstrated. In the light of this knowledge, a variation of the treatment of severe burns is here presented.

With the introduction of the tannic acid treatment of burns by Davidson in 1925,[2] there was a sharp decline in the mortality and morbidity rates associated with severe burns. Subsequently, many variations of the method were employed. Most of these were aimed in particular at tanning the burned area, although dyes which combined tanning action with bacteriostasis were widely employed.

In 1925, Davidson [2] advocated the application of 2.5 per cent solution of tannic acid to produce a tough membrane over the burned areas. The design was to prevent the loss of fluid and protect the raw surface against infection. It was found that infection readily developed beneath the eschar and that there was much scarring in the areas to which the tannic acid was applied. It is widely held also that the tannic acid eschar destroys small islands of epithelium which were not completely destroyed by the thermal injury.

In 1929, Firor and Aldrich [3] introduced the gentian violet treatment. They suggested that the toxemia of burns arises from infection. They therefore employed a bacteriostatic agent, namely, gentian violet, in their

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1. Mowlem, R.: The Treatment of Burns, Proc. Roy. Soc. Med. **34**:221, 1941.

2. Davidson, E. C.: The Tannic Acid Treatment of Burns, Surg., Gynec. & Obst. **41**:202, 1925.

3. Aldrich, R. H.: The Story of Burns, New England J. Med. **208**:299 (Feb. 9) 1933.

therapy. Finding that the gentian violet inhibited only the gram-positive organisms, Aldrich,[4] in 1933, added brilliant green and neutral acriflavine to the gentian violet and found more effective bacteriostasis resulting therefrom. The dyes have been found to be far more effective than tannic acid in the prevention of infection, and they have an additional advantage of producing a light tough flexible eschar in contrast to the heavy rigid tannic acid eschar.

Other procedures, such as pressure saline dressings, saline baths,[5] silver nitrate and cod liver oil,[6] have been used and modified extensively, but with such excellent treatises on the subject of burns as Harkins' "Treatment of Burns" [7] it is superfluous even to enumerate the various types of treatment.

With the increasing use of sulfanilamide and its derivatives in infections of various sorts, it is not surprising to find these drugs taking a place in the therapy of burns. In 1941, Pickrell [8] reported a series of cases in which burns were treated with 3 per cent solution of sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) in 8 per cent solution of triethanolamine. Unusual in his treatment is the fact that the burned areas are not washed. Débridement is effected, and sulfadiazine is then sprayed over the burned area. This forms a thin transparent membrane over the surface and is an effective bacteriostatic. Absorption of the drug was rapid at the onset but ceased when the eschar formed. In none of Pickrell's cases did the drug reach toxic levels in the blood.

Hooker and Lam [9] reported 8 cases of burns treated with powdered sulfanilamide. In 5 of these cases, blood concentrations of from 1.0 to 4.5 mg. per hundred cubic centimeters were obtained. In 3 cases, significantly higher levels were obtained as follows:

From a burn measuring 15 by 4 cm., 9.4 mg. per hundred cubic centimeters
From a burn measuring 8 by 6 cm., 7.8 mg. per hundred cubic centimeters
From a burn measuring 30 by 60 cm., 33.0 mg. per hundred cubic centimeters

Although the significance of hemoconcentration in severe burns has been long recognized, it was not until 1936 that the full importance of

4. Aldrich, R. H.: The Role of Infection in Burns with Special Reference to Gentian Violet, New England J. Med. **208**:299, 1933.

5. Blair, V. P.; Brown, J. B., and Hamm, W. J.: The Early Care of Burns and the Repair of Their Defects, J. A. M. A. **98**:1355 (April 16) 1932.

6. Hardin, P. C.: The Cod Liver Oil Treatment of Burns, North Carolina M. J. **1**:82, 1940.

7. Harkins, H. N.: The Treatment of Burns, Springfield, Ill., Charles C. Thomas, Publisher, 1942.

8. Pickrell, K. L.: A New Treatment for Burns, Bull. Johns Hopkins Hosp. **69**:217, 1941.

9. Hooker, D. H., and Lam, C. R.: Absorption of Sulfanilamide from Burned Surfaces, Surgery **9**:534, 1941.

plasma loss was revealed by Weiner, Rowlette and Elman.[10] Previously, the local treatment of the burned areas was of primary concern to the clinicians. But with the advent of plasma banks, the role of fluid balance in cases of burns has become more fully appreciated and is now being placed in its proper light.

Many studies have been made concerning the fluid shifts which occur in burned areas. Suffice it to say that Davidson and Matthew [11] in 1927 showed that the fluid lost from the burned areas was plasma. Others have confirmed this. Underhill, Kapsinow and Fisk [12] demonstrated that the fluid loss occurred by way of damaged capillaries in the burned area. This fluid loss occurred primarily into the tissues and not externally. That this is the case has been effectively demonstrated by Elkinton, Wolff and Lee [13] in a study of 9 clinical cases of burns. They demonstrated that plasma restored the circulating blood volume but that physiologic solution of sodium chloride was ineffective in this respect.

From previous studies, therefore, it has become evident that replacement of plasma is the most important consideration in cases in which extensive tissue damage has permitted the escape of this portion of the blood. Physiologic solution of sodium chloride is unable to effect any lasting reduction of hemoconcentration. It merely increases the local tissue edema and augments hypoproteinemia by washing the plasma proteins out into the tissues. Oral ingestion of large amounts of water may lead to depletion of tissue electrolytes. Harkins [7] compounded a rule which is an effective guide to the administration of plasma. He advocated the use of 100 cc. of plasma for every 1 per cent rise in the hematocrit reading above the normal of 44 per cent. This rule does not take into account the existing level of the plasma proteins, whereas Elkinton, Wolff and Lee [13] devised a method for the direct determination of plasma requirement by means of a formula using the body weight, the plasma protein level and the hematocrit determination. Their formula for the calculation of plasma protein deficit is as follows:

$$\text{Plasma protein deficit in grams} = 3.5W - \frac{W(100 - Ho)HnPo}{2(100 - Hn)Ho}.$$

In this formula W is the normal body weight; Hn, the normal hematocrit reading; Ho, the observed hematocrit reading, and Po, the observed plasma protein concentration.

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10. Weiner, D. O.; Rowlette, A. P., and Elman, R.: The Significance of Serum Protein in Therapy of Severe Burns, Proc. Soc. Exper. Biol. & Med. **34**:484, 1936.

11. Davidson, E. C., and Matthew, C. W.: Plasma Proteins in Cutaneous Burns, Arch. Surg. **15**:265 (Aug.) 1927.

12. Underhill, F. P.; Kapsinow, R., and Fisk, M. E.: Studies on the Mechanism of Water Exchange in Animal Organism, Am. J. Physiol. **95**:315, 325, 334 and 339, 1930.

13. Elkinton, J. R.; Wolff, W. A., and Lee, W. E.: Plasma Transfusion in the Treatment of the Fluid Shift in Severe Burns, Ann. Surg. **112**:150, 1940.

In general two simple clinical tests—the plasma protein content of the blood and the hematocrit reading—are invaluable in the management of plasma therapy in cases of severe burns. The degree of hemoconcentration can readily be followed by frequent determinations of the cell volume. Since the cell volume is not an index of plasma protein loss but merely of hemoconcentration, it is evident that determination of the plasma protein level is necessary as a guide to plasma replacement.

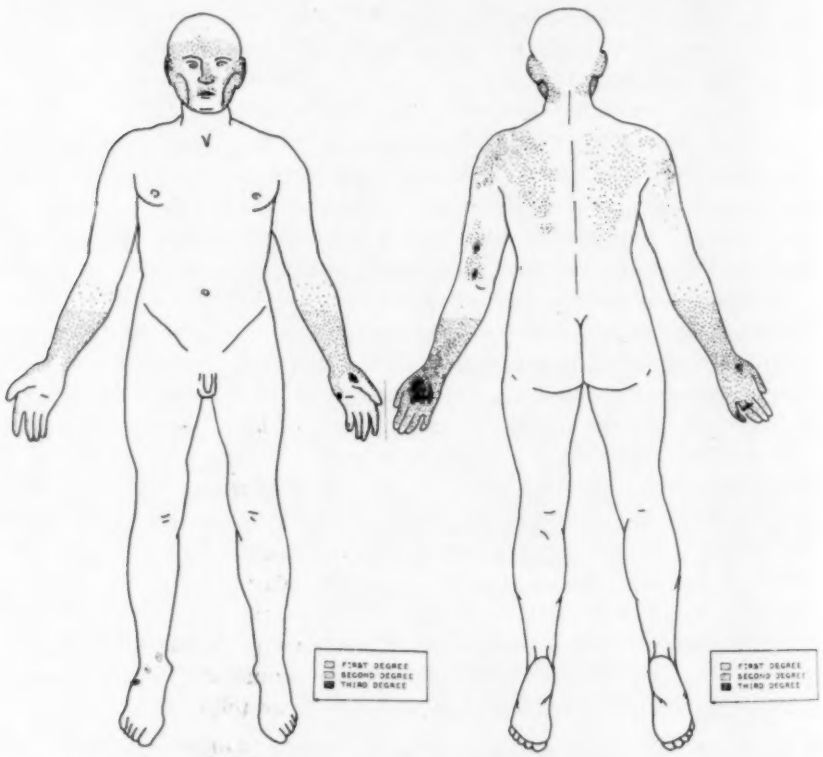


Fig. 1.—Extent of burns in patient H. G. The burned area was estimated at 27 per cent of the body surface.

Four patients were admitted to the Albert Merritt Billings Hospital on Oct. 27, 1941, fifteen minutes after an explosion and a fire in a chemical laboratory. The therapy employed is presented from the records of the 2 most severely burned patients. The illustrations reveal the extent and the nature of the burns and the fluid exchange and the blood findings observed in each case.

H. G., and E. O., healthy white men of 20 and 28 years of age, respectively, had extensive first, second and third degree burns about the face, the neck, the

hands, the arms and the back (figs. 1 and 2). The estimated burned surface area was 27 per cent on H. G. and 30 per cent on E. O. General physical examination was otherwise essentially negative. Morphine was given to each patient, and the clothing was removed. Intravenous administration of solution of sodium chloride was started, and the burned areas were débrided, cleansed with soap and water and copious amounts of physiologic solution of sodium chloride. After the injured parts were cleansed, they were dressed with sterile gauze heavily impregnated with 20 per cent solution of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) in an oxycholesterol-petrolatum base. The patients were then placed on

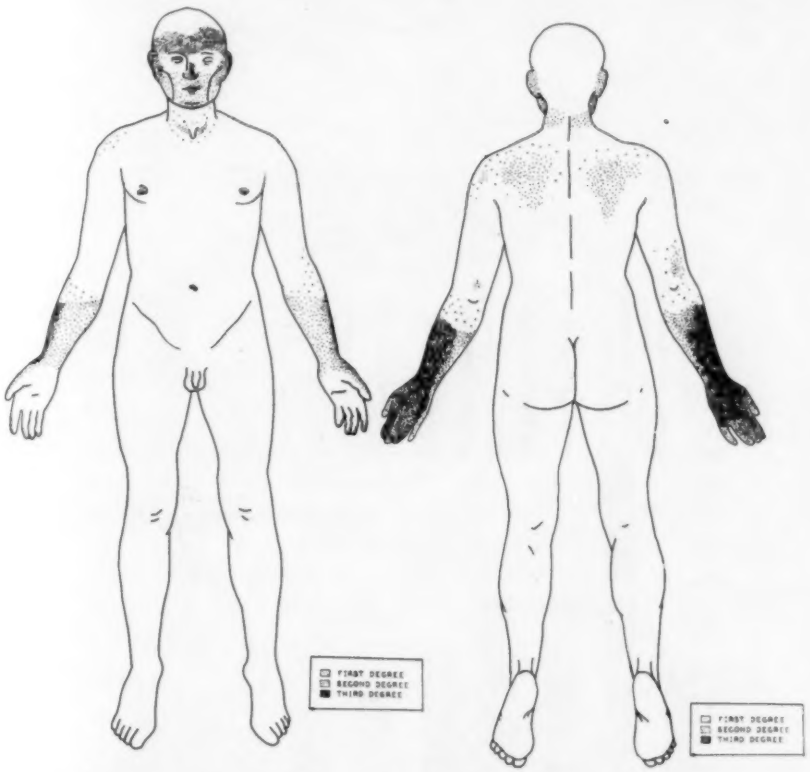


Fig. 2.—Extent of burns in the case of E. O. The burned area was estimated at 30 per cent of the body surface.

sterile sheets beneath heat cradles, and the intravenous administration of plasma was started. Within forty-five minutes to one hour following the application of the sulfathiazole ointment, the patients were free from pain.

Ten hours after the accident, E. O. complained of a dull aching pain in the midepigastrium, and a short time later he became nauseated and vomited 200 cc. of grossly bloody vomitus which was strongly acid. At this time a Levine tube was introduced into the stomach, and continuous aspiration was effected by means of a Wangensteen suction apparatus. Much relief was afforded the patient by this procedure, but because of the severe burns about the nostrils, the nasal tube

could be left in place for only a few hours at a time. Both patients were then submitted to modified ulcer management under which they remained for the first two weeks of hospitalization.

The following day, October 28, the sulfathiazole dressings of 1 patient (E. O.) were replaced with wet saline packs for a period of four hours, and then the

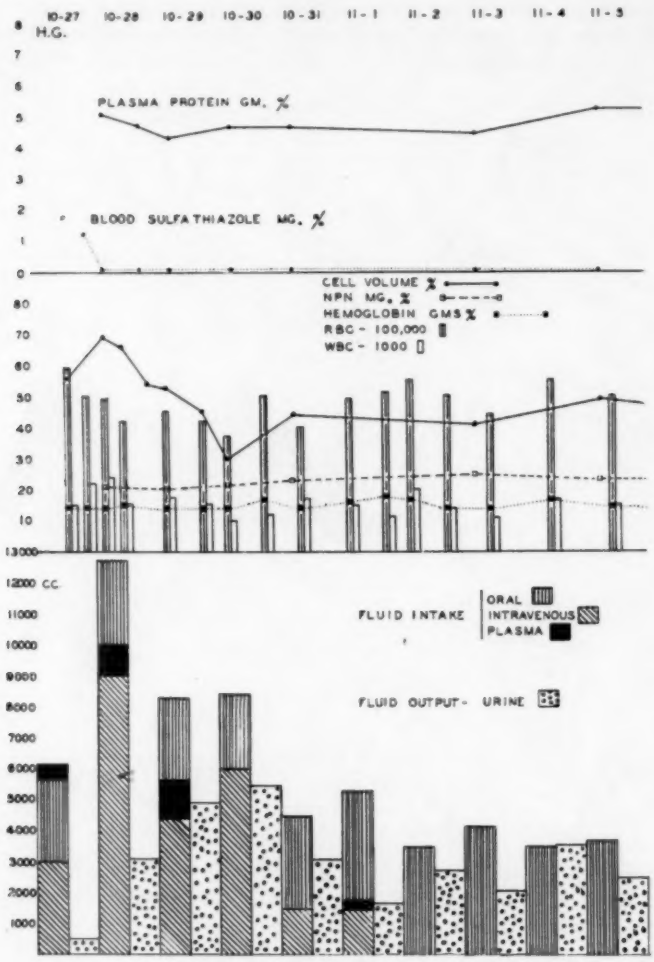


Fig. 3.—Chart of fluid exchange and variation of blood values in patient H. G.

ointment was reapplied. For four hours each day saline dressings were applied, but during the remainder of the time ointment dressings were in use. After the tenth day, continuous saline dressings were applied for the purpose of preparing the injured areas for grafting. Sulfathiazole dressings alone were employed on the other patient (H. G.) until the fourth day, when saline packs were applied as in the other case. Cultures taken from the burned areas of E. O. on the fifth day

yielded a growth of Staphylococcus albus, while it was not until the seventh day that positive cultures of the same organism were obtained from H. G. After four weeks, the dorsal surfaces of the forearms of E. O. were grafted with dermatome grafts, and a similar graft was placed on the dorsum of the left hand of H. G.

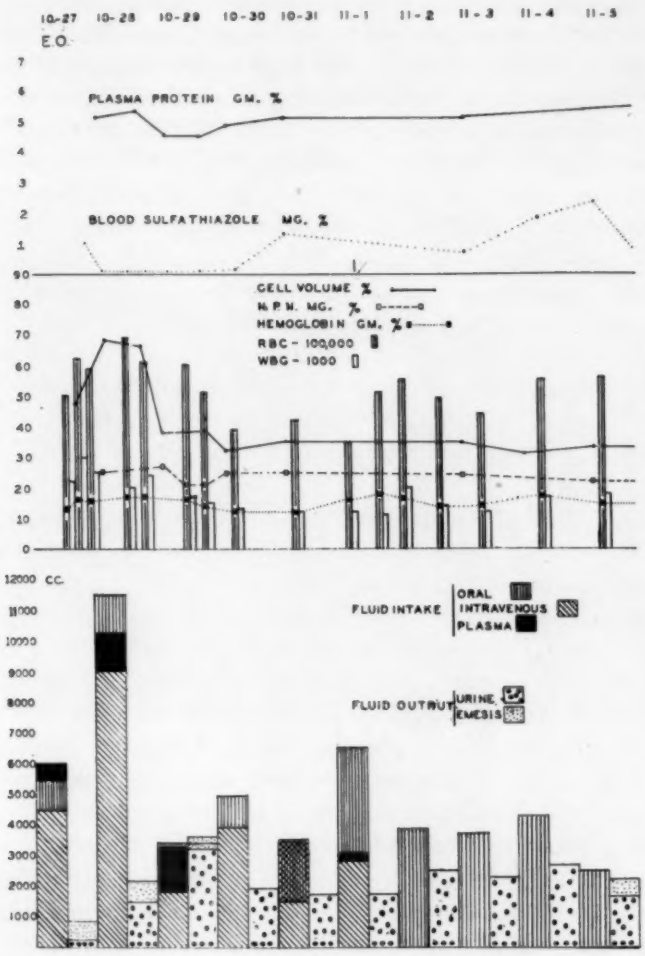


Fig. 4.—Chart of fluid exchange and variation of blood values in patient E. O.

The management of the fluid balance of these 2 patients is fully presented in figures 3 and 4. In retrospect, we must say that much larger volumes of plasma might well have been given during the first three days and considerably less solution of dextrose and sodium chloride. The high hematocrit values and the low plasma protein levels reveal that there was serious hemoconcentration and hypoproteinemia. Local tissue edema was extensive, suggesting that there was

not sufficient plasma protein osmotic pressure to retain the crystalloids in the circulating blood.

Recovery was remarkably rapid, and scarring was minimal. At the time of writing, the function of the hands is excellent, and although the fingers were severely burned, there is nowhere scar tissue contracture or limitation of motion.

The treatment here presented is of interest in that it sheds light on the benefits to be expected from the local use of sulfathiazole ointment in the therapy of thermal injuries. Pain is promptly alleviated. This was strikingly brought out by the fact that the patients pleaded for the return of the ointment following three or four hours of saline dressings. Infection is minimized, and scarring is apparently less severe. It is our feeling that remaining islands of epithelium are preserved and possibly even stimulated by the application of this chemotherapeutic agent.

Generally speaking, it is impossible to maintain a large denuded area in a sterile condition by the use of simple pressure dressings. Some bacteriostatic material is needed to maintain an aseptic field. This is particularly true in wartime, when a large number of patients must be treated by a small staff. With this consideration in mind, we propose the use of sulfanilamide and its derivatives in ointment form because of the bacteriostatic and analgesic effects of such a combination of chemotherapeutic agents.

Plasma loss may be minimized by the application of pressure dressings to the surfaces. Likewise, such dressings prevent to a considerable degree the edema accompanying such injuries as extensive burns. Coagulation of the weeping surfaces also has been successful in reducing the plasma loss. However, pressure dressings are probably more desirable than coagulation of the burned area, for the reported experience with the coagulative methods suggests that much of the epithelium which would ordinarily survive is probably killed as a direct result of the tanning agent used. Furthermore, tanning fixes the viable tissues on the surface of the denuded areas, thus leading to somewhat more extensive scarring than would otherwise result.

Since June 1941, we have been employing a 20 per cent sulfathiazole ointment. Sulfathiazole was chosen as the chemotherapeutic agent because its range of effective bacteriostasis is wider than that of any of the other three sulfanilamide drugs currently employed. Of particular importance is its effectiveness against the common pathogens. The most desirable concentration for such an agent is as yet undetermined, but we have found that an ointment containing 20 per cent of sulfathiazole gives rise to no grossly harmful effects. The photograph of the burned areas (fig. 5) taken fifteen days after the time of injury discloses numerous islets of epithelial regeneration in the areas subjected to this ointment almost continuously for two weeks. Likewise, when this ointment is

placed on the donor site of a dermatome graft no evident retardation of epithelial regeneration has been noted.

In the choice of an ointment base three features were considered desirable. First, the base itself should be nontoxic. We chose one (aquaphor) that contains 5 per cent oxycholesterol (a substance contained in human sebum) and 95 per cent petrolatum. Second, it seemed advisable that an absorbent base should be employed, since such a base theoretically tends to minimize the absorption of the drug by the tissues. Third, the ointment base should permit intimate contact between the sulfathiazole and the local tissues. An oxycholesterol-petrolatum base, more than petrolatum alone, affords this characteristic because of its

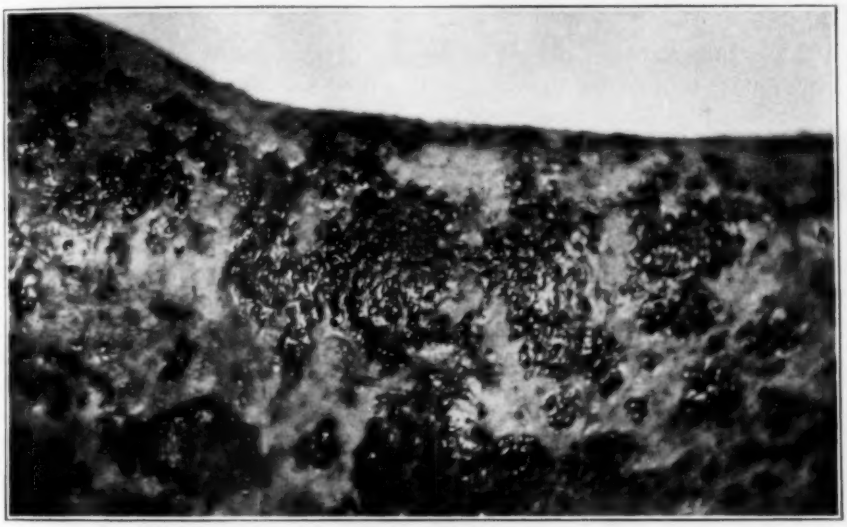

Fig. 5.—Photograph of healing surface of third degree burn taken fifteen days after injury.

hydroscopic nature. By fulfilling these requirements such a base seems to be suitable as an ointment base for sulfathiazole.

Absorption of sulfathiazole from the extensively burned areas in these 2 cases was minimal. Daily collection of urine failed to disclose excretion of more than 2.0 Gm. per twenty-four hours in 1 case (E. O.) and 1.5 Gm. per twenty-four hours in the other case (H. G.). Likewise, the total sulfathiazole in the circulating blood over the same period failed to exceed 1.5 mg. per cent, except in 1 case (E. O.), in which, for a short period, the drug was given by mouth. Since 1 pound (453.6 Gm.) of ointment (about 100 Gm. of sulfathiazole) was applied daily to each patient during the first week, it is readily apparent that the amount absorbed was negligible.

This ointment has been widely employed in the University of Chicago Clinics during the past ten months in the treatment of superficial ulcerating areas, abrasions and infected superficial wounds and in the impregnation of gauze packs used in various infected surgical wounds. By and large, the results have been gratifying in more than 150 cases in which the ointment has been employed. The greatest benefit has been observed in cases of infection by staphylococcus, streptococcus or Bacillus coli. The least benefit was derived by wounds infected with the common anaerobic organisms.

## SUMMARY

A brief résumé of the more important types of treatment of thermal injuries is given.

The importance of plasma in the care of such patients is emphasized, and guides to the administration of this fluid are presented.

Summaries of the case histories of 2 patients and the modes of therapy employed are presented together with studies of fluid balance, blood changes and urinary findings.

Sulfathiazole ointment compounded so that 20 per cent of the drug is contained in an oxycholesterol-petrolatum base is advocated for thermal injuries as well as for other cutaneous injuries.

# CHANGES IN THE BODY WATER PARTITION AND EXTRACELLULAR ELECTROLYTES IN SHOCK

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AND
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The present study is an attempt, using the methods available at the present time, to investigate the various changes in the extracellular and intracellular body water, the changes in the electrolytes of the extracellular fluid and the processes of the body in regulating the osmotic pressure of the intracellular and extracellular fluids and an attempt to interpret these changes in the light of presently accepted facts.

Recent studies on the pathogenesis and treatment of shock have dealt particularly with the decrease in plasma volume and the methods of restoring this lost volume. These studies satisfactorily demonstrated the nature and the extent of such plasma volume decrease.[1] The hemoconcentration which occurs in shock, as pointed out by Moon and Kennedy,[2] is a reflection of this decrease in plasma. Information on the phases of body water other than plasma during shock is almost lacking. Moon [3] maintained that in traumatic shock the tissue fluids, presumably interstitial water, are increased owing to widespread escape of plasma from the capillary bed. Dunphy and others,[4] however, from careful

From the Department of Pathology, Baylor University College of Medicine.

1. Keith, N. M., in Blood Volume Changes in Wound Shock and Primary Hemorrhage, Medical Research Committee, Special Report Series, no. 27, London, His Majesty's Stationery Office, 1919. Mahoney, E. B.: A Study of Experimental and Clinical Shock with Special Reference to Its Treatment by the Intravenous Injection of Preserved Plasma, Ann. Surg. **108**:178, 1938. Keeley, J. L.; Gibson, J. G., II, and Pijoan, M.: The Effect of Thermal Trauma on Blood Volume, Serum Protein, and Certain Blood Electrolytes: An Experimental Study of the Effects of Burns, Surgery **5**:872, 1939. Fine, J.; Fuchs, F., and Gendel, S.: Changes in Plasma Volume Due to Decompression of the Distended Small Intestine, Arch. Surg. **40**:710 (April) 1940.

2. Moon, V. H., and Kennedy, P. J.: Changes in Blood Concentration Incident to Shock, J. Lab. & Clin. Med. **19**:295, 1933.

3. Moon, V. H.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938.

4. Dunphy, J. E.; Gibson, J. G., II, and Keeley, J. L.: Observations on the Pathology of Experimental Traumatic Shock, Surg., Gynec. & Obst. **72**:823, 1941.

postmortem studies showed that this increase in tissue fluid occurs only late in the course of experimental burns and traumatic shock and that early the tissue fluids are not apparently increased (gross and microscopic observations). On the other hand, Moon[3] said that in hemorrhage the tissues and the body cavities are less moist than usual—apparently indicating a decrease in interstitial water. Blalock[5] indicated that in early traumatic shock and hemorrhage alike, the tissue fluids are decreased (interstitial water decreased). No recorded studies are available which indicate, in any quantitative degree, the changes in interstitial water, and there has been complete neglect of any consideration of the possible changes of intracellular water in shock or hemorrhage. As a matter of fact, studies of these two phases of body water in any circumstance have been scanty. Gamble and associates[6] were apparently the first to indicate the possibility of determining relative changes in interstitial and intracellular body water by determining the sodium and potassium balance of the body. Gilman[7] and Darrow and Yannet,[8] using this principle, calculated changes in interstitial water and intracellular water after sodium depletion following intraperitoneal injection of dextrose. Gamble and associates reported studies of these body water changes in children under various circumstances. The thiocyanate method of measuring extracellular fluids, introduced by Crandall and Anderson,[9] constitutes another means of measuring interstitial fluid and, indirectly, intracellular fluid. There is a distinct need for studies of the extracellular and intracellular phases of body water in shock. It is practically impossible satisfactorily to consider changes in body water without at the same time correlating or supplementing with electrolyte studies—particularly studies of sodium and potassium—the chief cations of extracellular and intracellular fluids, respectively. These ions are of significance not only as indicators of body water changes but also as indicators of the body economy in maintaining an equal osmotic pressure inside the cell and in the fluid environment of the cell. Further, in an attempt to understand

5. Blalock, A.: Principles of Surgical Care: Shock and Other Problems, St. Louis, C. V. Mosby Company, 1940.

6. Gamble, J. L.; Ross, G. S., and Tisdall, F. F.: The Metabolism of Fixed Base During Fasting, J. Biol. Chem. **57**:633, 1923.

7. Gilman, A.: Experimental Sodium Loss Analogous to Adrenal Insufficiency: The Resulting Water Shift and Sensitivity to Hemorrhage, Am. J. Physiol. **108**: 662, 1934.

8. Darrow, D. C., and Yannet, H.: The Change in the Distribution of Body Water Accompanying Increase and Decrease in Extracellular Electrolyte, J. Clin. Investigation **14**:266, 1935.

9. Crandall, L. A., Jr., and Anderson, M. X.: Estimation of State of Hydration of the Body by the Amount of Water Available for the Solution of Thiocyanate, Am. J. Digest. Dis. & Nutrition **1**:126, 1934.

the processes by which the body economy acts in this regard, a study of kidney tubular reabsorption of water and the cations is necessary. No information in this regard is avaliable for the condition of shock and hemorrhage. Scudder, Smith and Drew [10] drew attention to the terminal increase in plasma potassium in shock. Other investigators [11] failed to confirm this observation adequately.

## METHODS

Dogs were used in all experiments. Samples of blood were obtained from the jugular vein without stasis, and heparin was used as the anticoagulant. Anesthesia was produced by the intravenous injection of soluble pentobarbital, which was seldom repeated after the initial anesthetic dose. Blood pressure was measured by a mercury manometer connected with the carotid artery. Blood volume studies were rather unsatisfactory. The method of Gregersen, Gibson and Stead [12] was used. However, the irregular disappearance of the dye during shock and the almost constant hemolysis despite intense precautions greatly reduced the accuracy of this method. Original volume levels were calculated by this method, however, and subsequent changes were determined by changes in the hematocrit value, the often repeated criticism [13] being remembered that red blood cells are added to the circulation from the reservoir of the spleen. Extracellular water was calculated as the water available for solution of sodium thiocyanate according to the method of Crandall and Anderson.[9] Thiocyanate determinations were carried out by the method of Lavietes and others,[14] except that a lumetron photoelectric colorimeter was used to measure the color. Interstitial fluid volume was calculated as the difference between extracellular water and plasma volume. Intracellular water was calculated before shock as 42.5 per cent of body weight, while after shock it was calculated from the total increase or decrease of extracellular water, taking into account the fluid lost during the development of shock, which was measured in each experiment. Hemoconcentration studies, consisting of red blood cell count, hemoglobin estimation, hematocrit evaluation and determination of the specific gravity of whole blood and plasma, were also carried out at intervals during the course of the experiment.

10. Scudder, J.; Smith, M. E., and Drew, C. R.: Plasma Potassium Content of Cardiac Blood at Death, Am. J. Physiol. **126**:337, 1939.

11. Bisgard, J. D.; McIntyre, A. R., and Osheroff, W.: Studies of Sodium, Potassium and Chlorides of Blood Serum in Experimental Traumatic Shock, Shock of Induced Hyperpyrexia, High Intestinal Obstruction, and Duodenal Fistulas, Surgery **4**:528, 1938. Greenwood, W. F.; Haist, R. E., and Taylor, N. B.: The Plasma Potassium Following Intestinal Obstruction in Dogs, ibid. **7**:280, 1940.

12. Gregersen, M. I.; Gibson, J. J., and Stead, E. A.: Plasma Volume Determination with Dyes: Errors in Colorimetry; Use of the Blue Dye, T-1824, Am. J. Physiol. **113**:54, 1935.

13. Stead, E. A., Jr., and Ebert, R. V.: Relationship of Plasma Volume and the Cell-Plasma Ratio to the Total Red Cell Volume, Am. J. Physiol. **132**:411, 1941.

14. Lavietes, P. H.; Bourdillon, J., and Klinghoffer, K. A.: The Volume of the Extracellular Fluids of the Body, J. Clin. Investigation **15**:261, 1936.

Sodium analyses were carried out on blood and urine, the method of Butler and Tuthill being used,[15] while potassium analyses were done by the method of Truszkowski and Zwemer.[16] Urine was obtained through suprapubic catheter in male dogs and through urethral catheter in female dogs. The bladder was washed twice with distilled water before each collection period. Glomerular filtration was calculated by creatinine clearance[17] after the blood creatinine level had been increased by the intravenous injection of creatinine. All analyses were made on heparinized plasma. Using the information available from these blood and urine studies, the tubular reabsorption of water, sodium and potassium was calculated.

Shock was produced by three separate methods: (1) by the intraperitoneal injection of 25 cc. of 25 per cent sodium chloride per kilogram of body weight,[18] (2) by hemorrhage and (3) by trauma to the left hindleg with a blunt hammer. In the dogs shocked by the intraperitoneal injection of fluid, the lost extracellular fluid was calculated by subtracting the volume of fluid injected from the resulting peritoneal fluid. In dogs shocked by hemorrhage, careful measurements were kept of blood removed for sampling as well as that removed to produce shock. In dogs shocked by trauma, the lost fluid was determined by weighing the normal and traumatized legs after bisection according to the method of Blalock.[5]

## RESULTS

Table 1 indicates the changes in the various partitions of body water before and after shock in each of the 16 dogs. It will be seen that, with 2 exceptions, the plasma volume was greatly reduced. The reduction was greatest in the dogs shocked by intraperitoneal saline solution, intermediate in traumatic shock and least in hemorrhagic shock. The interstitial water changes, with but few exceptions, were distinct, indicating a striking increase in dogs shocked by saline solution, a decrease in dogs shocked by hemorrhage and an increase in 2 dogs and a decrease in 1 dog shocked by trauma. The intracellular water behaved in an opposite manner, decreasing after saline shock, increasing after hemorrhagic shock and decreasing after traumatic shock. The changes in the size of red blood cells, as shown by mean corpuscular volume, practically invariably corresponded directly, if not proportionally, to the intracellular fluid change.

Table 2 illustrates the changes brought about in the concentration of sodium and potassium in the extracellular fluid and urine as produced

15. Butler, A. M., and Tuthill, E.: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, J. Biol. Chem. **93**:171, 1931.

16. Truszkowski, R., and Zwemer, R. L.: Determination of Blood Potassium, Biochem. J. **31**:229, 1937.

17. Rehberg, P. B.: Studies on Kidney Function: I. The Rate of Filtration and Reabsorption in the Human Kidney, Biochem. J. **20**:447, 1926.

18. Davis, H. A.: Acute Circulatory Failure (Shock) Following Sub-Cutaneous Injection of Hypertonic Sodium Chloride Solution, Proc. Soc. Exper. Biol. & Med. **43**:354, 1940.

TABLE 1.—*Changes in the Distribution of Body Water in Shock from Intraperitoneal Injection of Hypertonic Solution of Sodium Chloride, Hemorrhage and Trauma*

| Experiment | Plasma Volume | Change, Per Cent * | Interstitial Water | Change, Per Cent | Intracellular Water | Change, Per Cent | Mean Corpuscular Volume | Change, Per Cent |
|---|---|---|---|---|---|---|---|---|
| Saline shock; no hemoconcentration | 375 | | 1,471 | | 2,405 | | 64.5 | |
| | 416 | +11 | 1,756 | +20 | 2,211 | —10 | 60.0 | — 7 |
| Saline shock | 403 | | 1,897 | | 3,189 | | 78.6 | |
| | 115 | —70 | 1,925 | +1.5 | 3,065 | — 3 | 75.5 | — 4 |
| Saline shock | 682 | | 2,889 | | 5,037 | | 67.2 | |
| | 193 | —71 | 3,065 | + 6 | 4,861 | — 3.5 | 57.5 | —15 |
| Saline shock | 326 | | 1,401 | | 2,362 | | 74.6 | |
| | 147 | —51 | 1,896 | +35 | 1,867 | —21 | 67 | —10 |
| Saline shock | 588 | | 1,339 | | 2,700 | | 71.5 | |
| | 253 | —57 | 1,677 | +25 | 2,362 | —12.5 | 64.7 | — 9.5 |
| Saline shock | 1,475 | | 2,046 | | 7,125 | | 76.1 | |
| | 587 | —67 | 3,333 | +39 | 5,838 | —18 | 72.7 | — 4.4 |
| Saline shock | 610 | | 1,049 | | 2,400 | | 86.1 | |
| | 172 | —70 | 1,541 | +48 | 2,098 | —13 | 66.5 | —22.5 |
| Shock by hemorrhage; initial hemoglobin, 10.15 Gm. | 972 | | 2,954 | | 6,460 | | 71.8 | |
| | 674 † | —32 | 2,510 | —15 | 6,914 | + 6.6 | 72.4 | + 0.8 |
| Shock by hemorrhage; initial hemoglobin, 9.5 Gm. | 1,620 | | 3,060 | | 5,950 | | 63.2 | |
| | 1,131 | —30 | 869 | —70 | 8,372 | +29 | 72.5 | +13 |
| Shock by hemorrhage; initial hemoglobin, 8.55 Gm. | 952 | | 2,818 | | 4,930 | | 63.1 | |
| | 388 | —59 | 2,317 | —18 | 5,487 | +11 | 73.2 | +13 |
| Shock by hemorrhage; initial hemoglobin, 12.95 Gm. | 625 | | 3,757 | | 3,612 | | 57.3 | |
| | 685 | + 9.6 | 1,008 | —45 | 6,271 | +70 | 60 | + 4.7 |
| Shock by hemorrhage; initial hemoglobin, 14.15 Gm. | 428 | | 1,365 | | 3,612 | | 64.8 | |
| | 169 | —60 | 1,932 | +29 | 3,528 | — 2.6 | 66.6 | + 2.8 |
| Shock by hemorrhage; initial hemoglobin, 13.25 Gm. | 600 | | 2,028 | | 2,890 | | 60 | |
| | 393 | —47 | 2,073 | + 2.2 | 2,845 | — 2 | 59 | — 1.7 |
| Shock by trauma; traumatized leg weighed +370 Gm. | 570 | | 3,218 | | 3,825 | | 72.5 | |
| | 288 | —50 | 3,627 | +11 | 3,273 | —14.4 | 69.8 | — 3.7 |
| Shock by trauma; traumatized leg weighed +385 Gm. | 530 | | 1,795 | | 4,250 | | 72.8 | |
| | 300 | —43.4 | 1,600 | —11 | 4,270 | 0 | 67.1 | — 8 |
| Shock by trauma; traumatized leg weighed +600 Gm. | 882 | | 2,284 | | 4,250 | | 62.1 | |
| | 473 | —46 | 2,700 | +18 | 3,824 | —10 | 56.6 | — 9 |

* Calculated by changes in hematocrit value.
† Measured by blue dye method.

TABLE 2.—*Changes in Sodium and Potassium in Extracellular Fluids and in Urine in Hemorrhage and Shock from Trauma*

| Experiment | Plasma Sodium, Mg. per 100 Cc. | Change, Per Cent | Plasma Potassium, Mg. per 100 Cc. | Change, Per Cent | Change in Interstitial Water, Per Cent | Urine Sodium, Mg. per Hour | Urine Potassium, Mg. per Hour |
|---|---|---|---|---|---|---|---|
| Shock by hemorrhage; | 319 | | 14.0 | | | .... | .... |
| severe | 342 | + 7.4 | 17.0 | +22 | —15 | | |
| Hemorrhage; | 322 | | 18.2 | | | .... | .... |
| mild shock | 336 | + 4.3 | 18.4 | 0 | —70 | | |
| Hemorrhage; | 277 | | 16.2 | | | 84.4 | 47.6 |
| mild shock | 316 | +12.0 | 14.3 | —12 | —18 | 0.56 | 11.9 |
| Shock by hemorrhage; | 324 | | 18.8 | | | 113.0 | 34.6 |
| severe | 307 | — 5.2 | 27.8 | +47 | +29 | 0.4 | 7.2 |
| Shock by hemorrhage; | 313 | | 19.2 | | | .... | .... |
| severe | 326 | + 4.1 | 25.6 | +33 | —45 | | |
| Shock by hemorrhage; | 315 | | 15.4 | | | 3.1 | 15.0 |
| severe | 329 | + 4.5 | 20.4 | +32 | + 2.2 | 0.1 | 0.5 |
| Shock by trauma; | 334 | | 23.6 | | | 6.5 | 2.8 |
| severe | 332 | 0 | 28.2 | +20 | +11 | 19.9 | 2.3 |
| Shock by trauma; | 283 | | 15.6 | | | 54.1 | 20.0 |
| severe | 311 | + 6.3 | 39.2 | +151 | —11 | 12.0 | 0.8 |
| Shock by trauma; | 357 | | 16.2 | | | 9.2 | 7.5 |
| severe | 327 | — 8.4 | 19.3 | +19 | +18 | 3.76 | 0.2 |

by shock from trauma and hemorrhage. In shock from hemorrhage, the plasma sodium showed, with 1 exception, an increase. Except in 1 instance this change in sodium indirectly corresponded to changes in interstitial water, i. e., when sodium increased, interstitial water decreased and the opposite also was true. The small number of experiments with traumatic shock renders conclusion difficult with regard to changes in plasma sodium in this condition. Table 2 demonstrates also a fairly constant, slight but definite increase in plasma potassium in both hemorrhagic and traumatic shock. In 2 animals in which the increase in potassium did not occur, the shock produced was mild, and the animals were killed.

TABLE 3.—*Glomerular Filtration and Tubular Reabsorption* During Hemorrhage and Shock*

| Experiment | Glomerular Filtration, Cc. per Hr. | Tubular Reabsorption | | |
|---|---|---|---|---|
| | | Water | Sodium | Potassium |
| Hemorrhage | 1,021 | × 28 | × 33 | × 35 |
| | 631 | × 53 | ×4,000 | × 7 |
| Hemorrhage | 2,130 | × 47 | × 64 | × 6 |
| | 310 | × 62 | ×3,000 | × 5 |
| Hemorrhage | 1,375 | ×147 | ×1,764 | × 18 |
| | 70 | × 70 | ×2,000 | × 25 |
| Traumatic shock | 1,440 | ×120 | × 742 | ×104 |
| | 190 | × 30 | × 32 | × 18 |
| Traumatic shock | 1,200 | ×100 | × 63 | × 9 |
| | 125 | × 50 | × 33 | × 25 |
| Traumatic shock | 3,324 | × 88 | × 46 | × 23 |
| | 92.5 | × 93 | × 120 | × 92 |

* Tubular reabsorption figures represent the ratio of glomerular filtrate values per hour to the urine values per hour.

The changes in glomerular filtration and tubular reabsorption in hemorrhagic and traumatic shock are indicated in table 3. It will be seen, as expected, that glomerular filtration falls sharply during shock. In shock from hemorrhage, tubular reabsorption of water is increased definitely, sodium reabsorption increased markedly, the sodium being conserved 2,000 to 4,000 times in its passage through the tubules, while potassium reabsorption tends to be decreased. Strikingly, in traumatic shock, this conservation of water and sodium is absent. Indeed, there tends to occur less reabsorption of these two constituents, while potassium is apparently conserved during traumatic shock.

Table 4 shows a comparison between plasma volume change and actual measured loss of plasma volume. Prominent differences between these values are evident, indicating either an error in the plasma volume

TABLE 4.—*Fate of Plasma Fluid and Interstitial Water in Shock from Intraperitoneal Injection of Hypertonic Solution of Sodium Chloride, Hemorrhage and Trauma*

| | Intraperitoneal Injection of Hypertonic Solution of Sodium Chloride | | | | | | | Hemorrhage | | | | | | Trauma | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Experiment | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| Measured lost plasma..... | 270 | 400 | 750 | 180 | 255 | 610 | 250 | 315 | 227 | 234 | 167 | 165 | 370 | 385 | 600 | 189 |
| Calculated decrease in plasma volume * | + 41 | 288 | 489 | 179 | 335 | 888 | 438 | 300† | 489 | 564 | + 60 | 519 | 282 | 230 | 400 | 297 |
| Fluid lost to or taken from interstial water | —311 | —112 | —251 | — 1 | + 80 | +278 | +178 | — 15 | +202 | +330 | —227 | +354 | — 88 | —155 | —181 | +100 |

* Measured by changes in hematocrit value.
† Measured by dye method.

calculations or passage of fluid between the interstitial water and the plasma as indicated in the table.

Table 5 is a further representation of these values in hemorrhagic shock as measured by the dye method. The found red blood cell volume and plasma volume levels are compared with the actual measured lost plasma and red blood cells. It will be noted from this table that the decrease in plasma and red blood cell volume is small in view of the fact that definite shock was produced in each instance by bleeding. This fact tends to cast some doubt on the method. However, there was constantly added, according to these studies, a distinct quantity of red blood cells to the circulating blood; further, fluid passed in every instance from the interstitial fluid to the plasma, both of which facts are in accord with present views.

TABLE 5.—*Plasma and Red Blood Cell Volume Changes After Hemorrhage* *

| Experiment | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|
| Red blood cell volume | 377<br>488 | 695<br>730 | 328<br>439 | 483<br>360 | 317<br>410 |
| Plasma volume | 972<br>674 | 1,620<br>1,485 | 952<br>761 | 625<br>655 | 428<br>540 |
| Measured plasma loss | 315 | 227 | 234 | 167 | 165 |
| Total red blood cell change † | +278 | + 158 | +227 | — 25 | +207 |
| Fluid passing from interstitial spaces to plasma | 17 | 92 | 43 | 197 | 277 |

* Measured by dye method.
† Measured loss plus increase in blood.

## COMMENT

It is necessary to account when possible for the various changes in the partition of body water, extracellular electrolytes and tubular reabsorption of electrolytes, either as direct results of the mechanical, physical and chemical defects of shock itself, or as compensatory efforts of the body processes in regulating the internal environment of the body.

In the dogs shocked by the intraperitoneal injection of hypertonic saline, an extrinsic factor, viz., the introduction of large amounts of sodium and chloride into the extracellular phase, must be taken into account. The passage of sodium ions in this manner must be anticipated since the sodium ion is freely permeable across the peritoneal and capillary membranes and since the osmotic pressure in the peritoneal fluid is vastly greater than that in the extracellular water. Consequently, as a result of this passage of sodium, the osmotic pressure in the extracellular water would be increased. The sodium ion would not be expected to pass into the body cells since the cell membrane is not permeable to sodium. Therefore the body cells would find themselves in a fluid environment with osmotic pressure greater than that in the cells them-

selves, and depending on laws of osmosis and semipermeable membranes, there would be a passage of water from cells to extracellular spaces. Apparently it is this phenomenon which accounts for the increase in interstitial water and the decrease in intracellular water which were found to occur in this type of shock. Apparently the red cells respond in a similar manner to this increased osmotic pressure of their surrounding fluid environment, the plasma, and therefore the red cell fluid decreases; this is shown by decrease in mean corpuscular volume.

In shock from hemorrhage, the changes in interstitial and intracellular water are of an opposite nature, the interstitial water decreasing and the intracellular fluid increasing. There is no reason to anticipate an alteration of the osmotic pressure of the extracellular water after hemorrhage, so that it becomes necessary to assume changes in the cell osmotic pressure in order to account for the change in partition of water. On examining table 1, it may be seen that in all dogs exhibiting marked increase in intracellular water after hemorrhage, the initial hemoglobin level was low. It is thought that in these animals a severe grade of anoxemia was produced by hemorrhage, owing to reduction of the red blood cell mass below the critical level for necessary oxygen transport and in excess of the anoxemia produced in animals with normal control hemoglobin levels. It has been repeatedly stated that anoxemia induces increased osmotic pressure within cells, and this phenomenon, occurring here, would be expected to cause a transit of fluid from the interstitial phase to the intracellular phase. The increase in mean corpuscular volume of the red blood cells in these same animals shocked by hemorrhage would indicate that the red blood cells respond to this situation in a manner similar to the body cells. In these animals, as water passes from extracellular to intracellular phase, unaccompanied by the sodium ion, an increase in the concentration of the sodium ion of extracellular fluids would be expected. Such an increase was found to occur in these experiments.

Why the body should conserve sodium and water after hemorrhage is easy to understand, since the necessity of retention of fluid of normal osmolar concentration is eminent. The means by which this process is brought about by the renal tubules involves considerably more difficult problems. The influence of the adrenal cortical hormone, pituitary hormones and the hypothalamus must be considered, in the light of present knowledge, as the likely regulators, acting together or individually. At least it appears certain that in hemorrhage this regulating or compensating process is available and active.

In traumatic shock, the changes in body water are less regular than after hemorrhage. The evidence is that in traumatic shock interstitial water increases while intracellular water decreases. We are at a loss to account for this difference from hemorrhagic shock. It is possible

that the cell membrane permeability is altered in this type of shock, either under the influence of deficient cortical hormone or as a result of a direct action of some toxic material formed as a result of trauma. Further evidence that some such influence is active is afforded by the studies of tubular reabsorption of water and electrolytes in traumatic shock. The results of this study show a failure of the tubules to conserve sodium or water over the control levels. On the other hand, it may be felt that in traumatic shock there exists an essential difference from hemorrhage in that the fluid lost from the extracellular spaces is not actually lost from the body, nor is sodium lost from the body, and consequently no need for conserving the materials arises.

Although the results of these studies indicate a decrease in interstitial fluid in shock from hemorrhage accompanied by anoxemia and an increase in the interstitial fluid in traumatic shock, it should be reemphasized that these changes take place only partly between plasma and interstitial fluid but largely between the interstitial and the intracellular fluid.

The behavior of potassium in shock has been the source of abundant speculations. Since potassium is the main cellular cation, explanations for the changes in potassium should take into account the physicochemical processes of the cell. In the present studies, it was a notable fact that potassium of the extracellular fluid did not increase until terminally. This terminal increase in potassium in hemorrhagic and traumatic shock may well be the result of a final severe injury of the cell membrane from anoxemia allowing potassium to pass more freely from the cell. It is probably more likely a compensatory effort of extreme type in which an attempt is made to reestablish an equilibrium between the osmotic pressure within the cell and in its internal environment, the extracellular water. As for the tubular reabsorption of potassium there is evidence that the change from before to during shock is in a manner opposite to that of tubular reabsorption of sodium. Further, there is reason to believe that when cellular osmotic pressure is increased, there is decreased tubular reabsorption of potassium and that when cellular osmotic pressure is decreased (or extracellular osmotic pressure increased), there is increased tubular reabsorption of potassium.

## SUMMARY

An attempt has been made to investigate the changes in body water—extracellular and intracellular—during experimental shock. In shock from intraperitoneal injection of hypertonic solution of sodium chloride, excess sodium ions in the extracellular fluids raise the osmotic pressure of this phase, causing a transit of fluid from the cell to the interstitial fluid. Thus, an increase in interstitial water and a decrease in intracellular fluid occurs. In hemorrhagic shock, probably owing to increased osmotic pressure within the cell resulting from anoxemia, there is a

passage of water from the extracellular to the intracellular phase. In traumatic shock, for an unexplained reason, the cell water decreases and interstitial water increases.

The changes in the volume of body cells, as shown by the volume of intracellular water, corresponds directly with alterations in the size of red blood cells, i. e., with the mean corpuscular volume.

A parallelism between the concentration of sodium in the extracellular fluid and the volume of extracellular fluid was noted. As interstitial water increased, sodium concentration in the plasma decreased, while the opposite was likewise true.

During shock from trauma or hemorrhage there is striking reduction in glomerular filtration. Tubular reabsorption of water and especially of sodium is increased after hemorrhagic shock, while potassium reabsorption is decreased. In traumatic shock, tubular reabsorption of water and sodium is not increased but may be decreased, while potassium reabsorption tends to be increased. It is thought that these changes in renal tubular function may be related to the function of the adrenal cortex or other water and electrolyte regulators.

In hemorrhagic and traumatic shock a terminal increase in extracellular (plasma) potassium was noted. This is thought to represent an attempt, under the rules of osmosis and semipermeable cell membranes, to equalize intracellular and extracellular osmotic pressure or to represent a severe injury of cell membrane, perhaps due to anoxemia, with increase in cell permeability.

Mr. Fox Miller and Mr. J. W. Ackert assisted in carrying out this study.

# PREPARATION FOR OPERATION AND POST-OPERATIVE CARE OF THE PATIENT WITH CANCER

## REVIEW OF CONTEMPORARY ADVANCES AND ANALYSIS OF EXPERIENCES WITH CURRENT CLINICAL PROCEDURES

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As the prevalence of cancer increases in accordance with the increasing longevity and advancing age constitution of the general population and as the respective curative spheres of resective and radiation therapies become more sharply defined, the special problems besetting operation on patients with cancer loom larger. Studies in operative care most frequently have been directed toward the general run of operative patients, predominantly persons requiring emergency or elective procedures and constituting for the most part relatively good operative risks. The need for surgical advancement in the field of cancer, in which the prospects hitherto have been held among the least promising, assumes imperative proportions as malignant disease becomes numerically the second most frequent cause of death. There can be no question but that progress will be painstakingly slow, but increased emphasis on the surgical requirements of this clinical group of patients must be forthcoming if medicine is to accept the challenge of the increasing incidence and mortality rate of cancer.

As has been stated, many and perhaps the majority of these patients present in addition to the questions of formidable surgical approaches and technics, associated problems which are probably of greater direct importance in relation to operability and survival. Certainly operative risk and mortality and morbidity rates are more often dependent on these coincident factors than on technical surgical skill. Unlike most candidates for operation, the patient with cancer can in general be considered a chronically ill patient and by the usual standards a relatively poor surgical risk from the outset, requiring major operation of a type that would tax to the utmost the physical resources of a person in good health. However, the constantly increasing number of successful

From the surgical service of Brooklyn Cancer Institute.

operative procedures on patients with cancer bears witness to the desirable results attainable when adequate supportive therapy is afforded and indicates even greater possibilities as the surgical aspects of cancer receive greater emphasis. In this study, therefore, we have sought to focus attention on problems of surgical care pertinent in a greater or a lesser degree to the entire field of surgical procedures for cancer.

In attempting a comprehensive revision of operative care procedures as carried out in our own surgical service and to insure that treatment will be as inclusive as necessary without at the same time sacrificing thoroughness in concentration on details, we have adopted a standard simplified routine suitable for the management of operative patients in a municipal cancer hospital. Operative care outline charts permitting appraisal at a glance of the status of the patient and providing convenient access to all essential data at any time have been found indispensable. These are subjected to periodic modification to incorporate current advances of established merit.

## AGE

The majority of patients with cancer are well beyond the physical prime of life and fall into the age group of 50 to 65 years of age. Arteriosclerotic heart disease, pulmonary emphysema, impaired renal function and other degenerative disorders are prevalent at this age. Moreover, fibroblastic proliferation and the associated phases of tissue repair compare unfavorably with the healing powers of the young. However, age should not be generally accepted as a contraindication per se to operation, since biometric surveys reveal that the normal life expectancy of persons attaining the age of 60 is from ten to fifteen years. Livingston has pointed out that the potential life salvage in the cancer age group well warrants radical resections entailing a relatively high operative mortality rate. Large series of cases of elderly patients successfully operated on with low associated mortality rates are being reported in increasing and encouraging numbers. Johnson and Lombard stressed, however, the great risk entailed in operations for cancer prolonged over two hours, particularly on patients past 60.

## PHYSICAL STATUS

That some degree of degenerative heart disease and generalized arteriosclerosis and attendant deficient circulation exists in the average patient with cancer is a reasonable assumption. Careful appraisal of the cardiovascular status is therefore indicated, since in this group of patients poor circulatory efficiency renders thrombosis, shock and other

postoperative complications major risks. Routine electrocardiography is of particular value to the surgeon in determining operative risk, choice of anesthetic, election of single or multiple stage procedures and similar decisions. Measurement of renal and hepatic function and determination of vital capacity as routine precautions are most apt to afford data of definite importance to the surgeon. Diabetes, anemia, nephritis, prostatism, obesity and perhaps sepsis, which are among the more frequent secondary pathologic entities concomitant to cancer, likewise demand special consideration in evaluating the surgical potentialities of the patient. The patient with any degree of nephritis, whether degenerative or inflammatory, is more susceptible to shock, and a smaller degree of collapse will cause fatal renal failure. In operation, numerous extrarenal factors, including reflex anuria and various types of shock, may result in death from renal failure in the absence of gross primary renal disease. Boyce pointed out that the tendency of surgeons to omit or ignore tests of hepatic function is to overlook the fact that, despite their limited precision, the information these tests afford may prove invaluable, since it is far easier to bolster a damaged liver threatened by anesthesia or anoxemia than a defective kidney or heart.

## PREOPERATIVE PREPARATION

The body tissues must be adequately supplied with fluid and electrolytes; metabolism and nutritive reserves of the organism must be restored to as close to normal levels as possible; the respiratory mechanism and the circulatory system must function at their greatest efficiency; the gastrointestinal organs must be in the best possible condition, and the central and autonomic nervous systems should serve under no avoidable handicap. Probably each of the foregoing factors, however, will necessitate some degree of corrective therapy in the average patient with cancer, and several, therefore, merit detailed discussion.

*Nutrition.*—While in the majority of cases in which operation is done, preoperative care in the main has been considered to devolve on adequate water and salt balance, the crux of supportive therapy in operation for cancer is the establishment of optimal nutrition. It is our usual experience to have patients with cancer enter the hospital after varying degrees of loss of weight. That this postulates ketogenic acidosis, depletion of glycogen and hypoproteinemia to prevail in the average case of cancer in which operation is performed is a matter deserving of far greater general recognition and attention, for each has been conclusively demonstrated to interfere with wound healing and to predispose to operative shock.

In a recent series of 100 unselected consecutive patients admitted to the Brooklyn Cancer Institute on whom operation was contemplated, the following illustrative findings were noted:

Total Blood Proteins:

Normal range: 6.5 to 8 mg.—Below 6.5 mg., 55 per cent
Above 7.5 mg., 10 per cent

Reported range: 3.3 to 9.6 mg.—Repeatedly below 7 mg., 73 per cent

(Only patients with values above 7 mg., in the absence of dehydration are considered by us to have a probably adequate protein reserve.)

In another group of 50 consecutive determinations of carbon dioxide made on newly admitted patients, these data were obtained:

Carbon Dioxide-Combining Power:

Normal range: 53 to 77—Below 45, 17 per cent
Marked tendency to alkalosis

Reported range: 30 to 79—Below 53, 58 per cent

It should be noted that the average value of total proteins discovered among our patients with cancer approximated the "critical level of edema" described by several authors. Ravdin demonstrated that hypoproteinemia is an important inhibiting factor in wound healing, that edema develops at the suture line in enteroanastomosis, resulting in a lack of tissue fusion, and that wound disruption likewise is associated with this deficiency of protein. Hartzell, Winfield and Irvin noted that serum protein and ascorbic acid values in cases of wound disruption are decidedly lower than normal. The frequency of wound disruption after operations for cancer is notable. In several cases at the Brooklyn Cancer Institute, the total protein level ranged from 4.9 to 5.2 mg., thus apparently confirming Ravdin's hypothesis. Maintenance of liver function and its protection against anesthetic and toxic injury, heretofore accepted as primarily dependent on adequate administration of carbohydrates, was likewise shown by Ravdin to be enhanced by a high protein and carbohydrate and low fat diet. It was his concept, in accordance with that of several other workers, that a lowered serum protein level is generally associated with damage to the liver and injury to the hepatic plasma protein regenerative mechanism rather than with simple protein malnutrition. Likewise important is the role played by hypoproteinemia in the causation of both peripheral and visceral edema, particularly pulmonary, as well as by the associated inhibition of gastrointestinal activity, which may, especially after enterostomy, favor the progress of adynamic ileus and increased predisposition to shock.

We find, as have others, that the most desirable practice is the administration of a 3,000 calory diet, consisting roughly of 70 per cent carbohydrate, 25 per cent protein and less than 5 per cent fat, resulting

in a nonketonic acid residue to favor healing. Tissue regeneration and cellular proliferation can hardly be anticipated without proper nutrition, and since it must be recognized that absorption and assimilation of abundantly provided nutrients, vitamins and minerals may be defective in cachectic patients with cancer, whenever parenteral administration is of demonstrable supplementary value, it should be employed. In instances of parapyloric obstruction, sterile, partly digested protein-carbohydrate or multiple aminoacid–carbohydrate nonresidue preparations, such as several commercial vitamin-reenforced products now marketed, are best administered by orojejunal tube feeding. Ice cream mix provides an admirably proportioned base to which vitamins may be added. Repeated plasma infusions or, if plasma is unavailable, blood transfusions to raise the serum proteins to normal values are frequently required. It has been shown that 500 cc. of plasma daily is sufficient to maintain nitrogen balance.

The Miller-Abbott tube or a modification of it may be utilized in cases of obstructive lesions of the gastrointestinal tract for maintaining nutrition. In treating lesions of the pyloric level, drainage is carried out above, and feeding below, the site of obstruction. For lesions below the absorptive levels of the small intestine drainage is maintained at the point of block, and feeding, above this point. Parenteral administration of protein (e. g., casein) hydrolysates and amino acids appears feasible and promising. Falconer found that a rise in the blood urea content indicates increased endogenous protein metabolism in cases of intestinal obstruction and thus serves as an index to the condition of the patient.

Holman, Whipple, Hartzell, Snell and others recently drew attention to the important surgical roles of vitamin and protein factors in postoperative recovery. Snell emphasized that dangerous avitaminosis may be precipitated in many persons because of long illness and limited diet when the insults of anesthesia, surgical procedures and further reductions in food intake in the postoperative period are added. Thus Yavorsky found on analysis that tissues and organs of all patients over the age of 46 years were lacking adequate amounts of vitamin C. Hartzell demonstrated that patients with malignant growths of the gastrointestinal tract have low vitamin C values. The metaplasia of epithelial structures, their poor healing response and the impaired resistance to infection of the skin and the respiratory and gastrointestinal mucosas attendant on avitaminosis must receive full consideration from the surgeon. Crile expressed the opinion that the parotitis after operation on the colon is related directly to insufficiency of vitamin A. In addition to being required for proper maintenance of heart and neuron axis function and gastrointestinal tone, vitamin B components appear essential for blood regeneration. Furthermore, as vitamin $B_1$ is a coenzyme in the metab-

olism of dextrose, administration of large amounts of carbohydrate parenterally has been reported to result in acute shortage of this vitamin, requiring, therefore, an adequate vitamin $B_1$ complement. Mackie cited several cases of malignant disease with deficiency of vitamin K in the absence of jaundice, a subject which will be more fully discussed later. Vitamin P, or citrin—the recently announced purpura-preventitive factor—appears to be related to the integrity of capillary membrane action and thus plays its role in the healing process.

The safe surgical assumption, since patients with cancer as a group are both middle aged and suffering from inanition, is that cancer presupposes surgical avitaminosis. Modern concepts of adequate preoperative preparation then require that an adequate reserve of vitamins be built up routinely before operation is undertaken on any patient with cancer. Spies stated pointedly that malnutrition tends to be associated with mixed rather than single deficiency diseases and indicates a simultaneous lack of calories, protein, calcium, phosphorus, iron and at least several vitamins. Butt and Leary repeated that massive doses are generally required to counterbalance serious depletions of the vitamins.

*Fluid and Electrolyte Balance.*—In patients with cancer the problem of restoring fluid and electrolyte balance frequently assumes more complex dimensions than in the everyday operative patient in whom routine administration of several liters of parenteral fluids has often sufficed despite a lack of consideration for individual needs. Fluid and electrolyte imbalance should be assumed to exist in patients with cancer until carefully ruled out, particularly in face of the fact that gastrointestinal lesions account for the majority of cases in which operation is accepted as the foremost means of therapy. It is in dealing with patients in this category that a history of protracted vomiting, diarrhea, starvation or obstruction with attendant dehydration and loss of electrolytes is so frequently elicited, and it requires carefully planned measures to combat them effectively.

In our service the whole blood chlorides were found among 100 patients on admission to the hospital to range from 396 to 742 mg. (The normal whole blood chloride range is from 430 to 520 mg.) Among our patients on admission to the hospital 45 per cent had whole blood chlorides below 450, and 60 per cent, below 475 mg. Only 18 per cent had whole blood chlorides above 500 and probably had a dependably adequate chloride and sodium reserve. Hypochlorinemia, then, is a common finding in candidates for operation for cancer.

Clinical dehydration exists when approximately a 6 per cent loss of body fluids occurs. In instances of losses of body water exceeding 10 per cent of the total, death may ensue. Moreover, dehydration is

generally accompanied by a deficiency in body electrolytes with resultant acidosis or alkalosis, since the major avenues for fluid depletion contribute equally toward coincident diminution of salt reserves.

For the proper maintenance of the balance between fluid intake and output, the ordinary salt requirement is only about 5 Gm. daily. Fluid imbalance supervenes if there is a disturbance of intake, output or retention mechanisms of either water or salt or both. If salt is in excess, the kidneys conserve water; this results ultimately in tissue edema. If salt is lost, however, e. g., by vomiting, the kidneys excrete water with consequent dehydration and hemoconcentration. Newburgh demonstrated that the average nitrogenous waste material excreted by the kidneys amounts to some 35 Gm. daily. A minimum of 500 cc. of urine at a specific gravity exceeding 1.030 is required to carry out this process of elimination. At a specific gravity of 1.010, that characteristic of filtrative, but for all practical purposes, nonreabsorptive kidney action, excretion of 1,500 cc. of urine daily satisfactorily takes care of nitrogenous catabolites.

The rule of Maddock and Coller that urinary output of operative patients should be maintained, if possible, at 1,500 cc. in twenty-four hours may therefore be taken to indicate adequate elimination at practically all ranges of kidney function. As a corollary, it has been pointed out that the patient under these circumstances is but exceptionally a subject for anxiety with regard to sodium chloride and water and acid-base balance. The healthy kidney is capable of excreting 35 to 40 Gm. of excessively administered salt daily. Beyond that amount, retention of salt and water occurs. The normal acid-base balance of the blood has for its important regulatory mechanisms the hemic carbonic acid and hemoglobin blood buffer and the chloride-shifting systems, the pulmonary exhalation of carbon dioxide and the excretion of renal ammonia and sodium phosphate. Within relatively narrow limits, loss of either the anions or the cations of the essential body electrolytes may be compensated for, e. g., by the renal shift to more alkaline phosphate excretion in the chloride loss of emesis, but protracted electrolyte loss leads to serious acidosis or alkalosis, depending on the nature of the predominant ions sacrificed; this is indicated by marked alterations in the carbon dioxide–combining power of the blood. An essential item in operative care charts is therefore a carefully itemized account of fluid and salt debits and credits.

Persistent emesis may often be an accompaniment of gastric or colonic disease. If the hydrochloric acid of a relatively normal gastric secretion is the major depletion, alkalosis supervenes. If the predominantly basic enteric secretions are repeatedly drained away in the

vomiting associated with obstruction low in the intestines, the more frequent syndrome of relative acidosis is encountered. Not infrequently, in the interim between stages of complicated surgical procedures profusely draining gastric, ileal or biliary fistulas may detract materially from the alkaline reserves. The use of Levine and Miller-Abbott tubes and Wangensteen suction drainage apparatus must frequently be resorted to, and all too commonly the added drain on body fluid and salt is overlooked. Since liquids and salt are both ingested and secreted in the upper part of the gastrointestinal tract but are probably dependent in the main for absorption and reabsorption on the normal function of the lower part of the ileum and the colon, great care must be taken lest combined oral feeding and suction drainage serve only to handicap the patient further by drawing into and away from the intestinal tract salt and water containing secretions well above the water-salt absorptive area, thus leading to even greater dehydration and acidosis. Since the salt loss by bowel normally is merely 0.5 Gm. and the water excreted in feces is less than 100 cc. daily, prolonged diarrhea also will signify uncompensated rectal diversion of considerable amounts of both fluid and electrolytes and impaired colonic absorptive activity. The normal skin excretion may be augmented to a marked degree by elevation of temperatures, increase of perspiration or profuse serous or purulent drainage.

In treating the majority of patients with acute or elective indications for surgical intervention, one is dealing with a local lesion and comparatively little general disturbance, requiring primarily the suitable adjustment of only salt and water. In the chronically ill, such as patients with cancer, inherent disturbances of normal sodium chloride and water retention mechanisms may require that these substances be given under strict scrutiny. The hypoproteinemia that has been shown to be characteristic presages increased susceptibility to edema. Casten and Bodenheimer described the plasma protein value of $5.5 \pm 3$ mg., not as a critical, but as a relative, edema level, depending on the intracapillary hemostatic pressure, the permeability of capillary walls and the salt-water partition as other major variables involved. Either impaired hepatic synthesis or malnutrition makes for a deficiency in the available labile liver protein. In marked instances of total base deficiency, another finding not rare among patients with cancer, Scudder, Peters and Gamble agreed that, owing to a mechanism as yet uncertain, maldistribution of sodium, chlorine and water may lead to untractable edema which is not influenced, unless the patient improves clinically, by giving the calculated requirements of salt and fluid. Administering sufficient plasma and sodium lactate to correct hypoproteinemia and make up the deficit in alkali may in favorable instances be followed by more normal regulation of salt and water.

*Fluids Administered.*—(*a*) Dextrose-Saline Solutions: Dextrose-saline solutions, generally as equal mixtures of 10 per cent dextrose and either 2 per cent or physiologic solution of sodium chloride are frequently ordered as a routine postoperative measure without proper respect for their actual indications. However, an important contra-indication to the prolonged use of dextrose-saline mixtures is the fact that in the absence of any deficiency of salt, an excess of sodium chloride may inadvertently be given. Four liters of a 5 per cent dextrose-saline solution contains about 20 Gm. of salt, four times the necessary ration of 5 Gm. daily. In the chronically ill patient with cancer whose kidneys are not functioning at maximum efficiency or with concomitant hypoproteinemia, edema is prone to ensue, particularly with the prolonged periods of parenteral administration of fluids usually required.

(*b*) Saline Solutions: Solutions of sodium chloride are required primarily to make up for proved deficits of sodium chloride. The normal sodium chloride requirement of 5 Gm. daily can be provided for by the liter of physiologic solution of sodium chloride given once a day. Since isotonic solutions are best tolerated and since fluid losses occur in isotonic quantities and, finally, since the value of hypertonic or hypotonic solutions is at best controversial, it is probably best to utilize isotonic preparations only, unless definite indications to the contrary obtain.

It is always important to maintain the blood chloride level above 450 mg., preferably at about 560 mg. Although several supposedly more exact methods of estimating the needed amount of saline solution have been proposed, the second clinical rule of Maddock and Coller has provided for us a yardstick that is easy to use, namely, for every increase of 100 mg. of blood chlorides desired, give 0.5 mg. of sodium chloride per kilogram of body weight. As a matter of practice, in a person of average weight, an increase of 100 mg. requires about 4 liters of physiologic solution of sodium chloride. Two to five days, depending on the quantities required, should be taken to make up the deficit, in accordance with the findings of Fantus that sick patients do not tolerate well the rapid intake of large amounts of fluid. Gamble demonstrated that solution of sodium chloride serves to make the adjustments necessary in the usually encountered degree of acidosis or alkalosis, since the healthy kidney will selectively excrete the sodium or the chloride ion depending on which is in excess. Several reports seem to indicate that Ringer's solution is less conducive to retention in the sick operative patient and is therefore to be preferred in difficult cases. Peters stated that small amounts of 2 or 5 per cent hypertonic solution of sodium chloride may prove to be of value toward raising the osmotic pressure of the plasma and withdrawing fluid from the tissues when sodium chloride appears to be bound to the interstitial fluid in the presence of

both hypochloremia and hypoproteinemia, although 25 per cent solution of dextrose in water is recommended if the blood chlorides are normal.

(*c*) Dextrose Solutions: Solutions of dextrose are preferably given in the isotonic 5 per cent strength. When additional carbohydrate for energy or for combating ketosis or liver damage is required, dextrose may be given in a 10 per cent solution. However, the urinary output must then be watched to insure that the hypertonic solution of dextrose does not result in transitory diuresis and consequent further dehydration. Given parenterally, 250 to 500 cc. per hour of 5 to 10 per cent solution of dextrose is oxidized as readily as if given by mouth and does not as a rule result in glycosuria. The water serving as the vehicle is then liberated for the normal fluid requirements of the body. It must be borne in mind, on the other hand, that prescribing dextrose solutions alone aggravates electrolyte deficiency coexisting with dehydration. Moreover, recent investigations showed that prolonged administration of dextrose solutions exclusively may precipitate acute avitaminosis B, since the vitamin B complex functions as a coenzyme in the intermediary stages of carbohydrate metabolism, unless vitamin B supplements are given. In the presence of clinical dehydration, when fluid by mouth cannot be ingested, approximately 3,500 cc. of a 5 per cent dextrose solution, to make up for the 6 per cent body fluid loss in a patient of average weight, is added gradually over several days to the 3,500 cc. daily metabolic requirement.

(*d*) Hartmann's Solution: Hartmann's solution as a 6 molar concentration of sodium lactate in Ringer's solution appears to be preferable to the likewise isotonic 5 per cent solution of sodium bicarbonate occasionally indicated as an emergency measure to combat extremes of acidosis or, by its buffering action, alkalosis.

The admonition to force fluids is often erroneously held to apply to postoperative care. In the middle-aged group, among whom the incidence of cancer is greatest, it must be realized that the indiscriminate addition of fluids parenterally carries the real threat of overtaxing the circulation and precipitating pulmonary edema or congestive heart failure or, exceptionally, acute cardiac dilation. Fluid given at a rate in excess of 15 cc. per minute has been demonstrated to accelerate the heart rate in young persons, and with diminished cardiac reserve it may cause pain or produce pulmonary edema. Fishberg stated that there is no appreciable increase in cardiac work below this rate, however, and indicated that it may be safely adopted as an upper limit in patients with cardiac disease or hypertension. Coller and Maddock pointed out that 250 to 500 cc. per hour is a safe rate which will not overload the normal heart. To forestall the onset of serious circulatory insufficiency, the patient should be repeatedly checked for a reactive rise in the pulse

rate and the blood pressure. The lung bases, the lower eyelids and the dependent portions of the body also should be examined several times daily for evidence of anasarca. Increased filling or distention of the peripheral veins, notably the jugular and the cubital, associated with the sudden appearance of cough or progressive dyspnea may indicate the onset of congestive heart failure. Surgical edema, then, because of the relative renal insufficiency of later life as well as the reasons previously mentioned, is somewhat more apt to occur in patients with cancer, who as a rule require prolonged parenteral administration of fluids. While subcutaneous edema may impair wound healing, pulmonary edema so induced may cause death.

Murphy, Correll and Grill recently demonstrated that isotonic solution of sodium chloride after four hours will still have produced an increase in plasma volume of one-fifth the volume of fluid administered regardless of the rate and that the addition of 8 grains (0.52 Gm.) of theophylline with ethylene diamine greatly diminishes this effect. Alternating this with a 5 per cent solution of dextrose likewise decreases both this tendency and that to increased venous pressure and to edema. Volumes exceeding 50 cc. of 50 per cent solution of dextrose, despite the addition of 8 grains of theophylline with ethylene diamine, failed, unlike the smaller amount, to improve pulmonary edema, cardiac dyspnea, decreased venous pressure or increased urinary output but on the contrary aggravated the condition of the patient, often precipitating cardiac failure. Mercurial diuretics by intramuscular injection in doses of 2 cc. or by suppository also may be used in the relief of edema. As an emergency procedure, phlebotomy and withdrawal of up to 500 cc. of blood may be indicated. Hypertonic plasma in 100 cc. quantities of a fourfold concentrate after the withdrawal of 500 cc. of blood appears to be a recently proposed effective remedy.

For routine purposes of maintaining fluid balance parenterally, we have adopted the following procedure in our service: If no loss of body fluid has occurred, 1,000 cc. of a 5 per cent solution of dextrose in distilled water is given by continuous intravenous drip over a period of two hours or of three hours in cases of suspected cardiac disease, in early morning and late afternoon. At noon, 1,000 cc. of physiologic solution of sodium chloride is given by hypodermoclysis into the thigh or directly into the vastus muscles, since pectoral infusions may hinder respiration. If pain is complained of, 25 cc. of 1 per cent procaine hydrochloride added to the solution of sodium chloride may give considerable relief. In the older patient, the subcutaneous route has several advantages, i. e., the relatively slow absorption is less apt to tax the circulation and poor absorption may be taken to signify impending edema or impaired circulatory function. Charted losses of body fluid are

replaced volume for volume by isotonic solution of sodium chloride or Ringer's solution. Unless urinary excretion is maintained at 1,000 to 1,500 cc. per twenty-four hours, blood and urinary chlorides, plasma protein and Van Slyke values are checked repeatedly for guidance in further therapy.

*Prevention and Treatment of Shock.*—Although considerable disagreement exists as to the exact pathologic physiology of shock, sufficient conclusive evidence concerning the contributory roles of inadequate blood volume, improper blood constituents and abnormal vascular tone to render their avoidance of maximum importance in the prevention of shock has been propounded. Moon depicted this sequence of events: Various noxious agents produce capillary atony; increased capillary permeability ensues, resulting in hemoconcentration and reduction in circulating blood volume, leading to tissue anoxemia. This leads to further capillary atony, establishing a vicious circle. The concomitant peripheral vasoconstriction and splanchnic vasodilation are still of controversial import. The toxic hyperpotassemia, emphasized by Scudder as indicative of profound cell injury, in Blalock's opinion plays a secondary part. Predisposing to an inadequate blood volume in the patient with cancer are the characteristically associated dehydration, chronic or acute blood loss, deficient plasma proteins and increased capillary permeability as a consequence of inanition, toxemia or the relative anoxemia of an impaired circulatory system and acapnia. It is wisest, therefore, to look on the average patient with cancer as specifically susceptible to surgical shock and to undertake the necessary combative measures as a routine precaution. Proper attention to nutritive requirements and plasma infusions to raise the serum proteins and specific gravity is doubly important in this regard. It may be roughly predicted that a liter of plasma will produce a rise of 0.2 mg. in the plasma protein level. The latter is best maintained above the value of 6.4. If hepatic protein regenerative synthesis is impaired, any gain may be lost after twenty-four hours, and frequent maintenance transfusions of plasma concentrates may prove essential. Needless to say, correction of acid-base imbalance and measures to minimize toxemia will tend to render capillary permeability more nearly normal. Except through the possible medium of extract of adrenal cortex, it has not been possible until the present specifically and directly to decrease capillary permeability. However, Hill quoted Krogh to the effect that concentrated plasma appears to improve vascular tone and the permeability of capillary walls. Measurement of the hematocrit value, the plasma protein and the plasma specific gravity are particularly invaluable procedures in the prophylaxis and early therapy of shock in the patient with cancer, in view of the latter's predisposition to this complication,

and should be routinely adopted in the management of this type of case. Falling hematocrit values demonstrate the necessity of blood transfusions and are suggestive of hemorrhage, while rising values indicate the hemoconcentration attendant on dehydration and early or impending shock and signify the necessity for fluid or plasma, respectively; if proteins drop without parallel similar change in hematocrit readings, protein plasma supplements are indicated, while if both hematocrit and plasma readings are low, whole blood may be given. Specific gravity determinations serve as a rapid check on the protein level of the blood and are easily performed at the bedside.

The standing orders in our service require that the patient shall never be left unattended during the first two hours and is to be kept under constant observation for shock and hemorrhage. Citrated blood (500 cc. to 1 liter) of compatible type is kept immediately available during and after the operation. Blood pressures are read every half hour for the first two hours, then at hourly intervals for four hours and thereafter two to four times daily for one week, with the mental reservation held to the fore that a marked fall in the blood pressure indicates relatively late advancing shock. Kekwick stipulated that 3 liters of blood or plasma may be required to elevate the blood pressure above 100 mm. in the patient in shock.

It should be pointed out that the common practice of confusing the problems of fluid-electrolyte balance and shock may prove to the considerable disadvantage of the patient with cancer. Peters and Blalock, among others, demonstrated that in patients in shock the administration of large amounts of solutions of sodium chloride or dextrose may serve temporarily to bolster the circulating blood volume, but thereafter the water given leaks rapidly into the tissue spaces, thereby washing still more proteins into the blood, or is rapidly eliminated by the kidneys, resulting in a more seriously handicapped patient than before, since the plasma volume and the osmotic pressure have been even further reduced and the interstitial fluid and the sodium chloride content increased. To combat shock by forestalling the increased fluid-electrolyte loss consequent to a prolonged surgical procedure calls for the essentially prophylactic administration by continuous intravenous drip of no more than 1 liter of solution of sodium chloride during the initial phase of the operation. Since the blood volume in shock or hemorrhage requires rapid restoration, this may be given at the rate of 20 to 40 cc. per minute until the pulse rate and the blood pressure improve. Additional amounts are harmful if this proves to be of no avail, and prompt substitution of continuous blood infusion at a rate determined by the depth of the shock reaction is called for. If no blood is immediately available, a 6 per cent acacia-Ringer's solution may serve, albeit undesirably, as a temporary expedient.

Recently, Scudder, Perla and several other investigators advocated the use of extract of adrenal cortex in the prevention and treatment of shock. In our hands, the initial results in a few cases have been inconclusive, but we are at present engaged in further study. It is held that this procedure enhances salt and water metabolism and tends to neutralize the hyperpotassemia reported to be present in shock. Several late studies seemed to indicate a marked superiority of extract of adrenal cortex, preferably in large doses, over desoxycorticosterone acetate, the synthetic preparation. A 5 per cent solution of sodium chloride, 300 to 500 cc., given intravenously appears to be of some value in treating prolonged shock to augment the action of a liter or more of blood or plasma in maintaining the blood pressure, if this begins to fall again. The specific value of solution of sodium chloride in the treatment of shock, according to Scudder, is that it may dilute the inspissated blood in hemoconcentration, increase the velocity of circulation, decrease the generalized vasoconstriction and increase the elimination of potassium through the kidneys.

We believe that routine postoperative assumption of the Trendelenburg position, by increasing the carotid and thus the cerebral circulation, as shown by Mann, is a worth while adjunct in both prevention and treatment of shock. Further, it is of value in precluding the aspiration of nasopharyngeal and bronchial secretions and vomitus. Recently, from the Mayo clinic there emanated the novel and ingenious suggestion that patients be kept in Fowler's position for three days before operation and thus accumulate a 1,500 cc. reserve of tissue fluid in the lower extremities. During operative procedures, assumption of the Trendelenburg position taps this reservoir, which, as an autotransfusion mechanism, prevents shock. Preventing the chilling of the patient by means of warm light blankets and hot water bottles is a frequently overlooked step directed against the development of shock. However, this must be done within limits not conducive to increased perspiration or marked peripheral vasodilation, for either will augment shock. Moreover, Blalock demonstrated that in experimental shock, once developed, the application of cold leads to longer survival than the application of heat.

Stimulative medication has proved in our hands to be relatively valueless in the therapy of shock, bearing out the thesis that restoration of circulating blood volume is the physiologically effective mode of therapy. In agreement with Fishberg and Tainter, we may state the sympathomimetic amines, notably, epinephrine and ephedrine (the latter given intravenously in emergencies as vasoconstrictors), seem serviceable to some extent but solely as temporary expedients for elevating the blood pressure. According to Best, pitressin, if administered prior to serum, results in less capillary leakage and a more sustained rise in blood pressure. However, camphor, strychnine and similar drugs appear to be

of no real worth, and digitalis is definitely contraindicated because of a tendency to increase peripheral vasodilation. Best and Solandt and Harkins questioned whether the physician may reasonably anticipate permanent recovery when blood pressure has fallen to the clinically low levels at which vasoconstrictors are used. Dunphy likewise stressed the irreversibility of advanced shock. The analeptic action of coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide), metrazol and picrotoxin in proper dosage in neutralizing the depressant action of prolonged anesthesia or of sedative and analgesic barbiturate preparations tending to deepen shock is acknowledged, but their place in the specific treatment of shock is difficult to evaluate. The administration of high concentrations of oxygen or of carboxygen (a mixture of carbon dioxide and oxygen), if acapnia or shallow breathing is present, seems, however, to provide material assistance to the patient with hemoconcentration, peripheral circulatory collapse and attendant tissue anoxia and should not be omitted.

Harkins was inclined to state that older patients may possess diminished compensatory adrenal potentialities and that their less pliable vasculature is less dependable for the maintenance of an adequate blood pressure in circulatory emergencies and are thereby more susceptible to shock. Intravenous giving of fluids as preventives and prompt administration of blood and plasma are the sine qua non of modern shock therapy, with oxygen and extract of adrenal cortex as promising adjuvants.

*Preventing Gastrointestinal Complications.*—In disturbances of the gastrointestinal tract amenable to amelioration before operation, steps toward this end should be taken, since restoration to relatively normal function lessens the likelihood of postoperative difficulties. In cases of gastric carcinoma, copious lavage with isotonic solution of sodium chloride is carried out the night before and repeated in the morning two hours before operation until returns are clear. One tenth per cent hydrochloric acid in physiologic solution of sodium chloride is used in the event of achlorhydria. When indicated, a Levine tube is left in situ for passage through an anastomotic stoma, as prophylaxis against distention and for initial fluid intake.

In cases of diseases of the colon and the rectum, irrigations of the colon with isotonic solution of sodium chloride are also carried out the night before and repeated on the morning of operation until returns are clean. In cases of obstructive growths of the sigmoid and the rectum an attempt is made to insert an indwelling rectal tube beyond the obstruction via a proctoscope for several days of preoperative high colonic saline irrigations. In some cases saline purges for several days before operation may be ordered, but purgation to the point of robbing the body of needed salt and fluid is avoided. By keeping infected gastric and

colonic content at a minimum, the obvious dangers of peritoneal spill when the lumen is entered are lessened. Moreover, restoration of normal peristalsis seems to have a worth while effect on the smooth muscle tonus of the digestive system. The method of relieving intestinal obstructions by means of suction drainge via a Miller-Abbott tube and the necessary precautions against coincident fluid-electrolyte waste have already been discussed. It seems that in cases of intestinal obstruction supervening on enteric neoplasms the value of conservative therapy has been safely established. It is necessary, however, to make certain of the vascular integrity of the bowel segments involved before placing primary dependence on a Levine or a Miller-Abbott tube.

Our routine in intestinal operations calls for limited administration of fluids by mouth after twenty-four to twenty-eight hours, preferably deferred until after flatus is passed freely. Sips only are allowed at first, thereafter 1 ounce (29.6 cc.) per hour may be given until 8 ounces (236.6 cc.) have been retained, and then increased amounts are allowed. As soon as permissible, the patient is allowed a soft fluid-like low residue diet high in vitamins and hematinic components. Foster, substantiated by Peters, showed that the gastrointestinal systems can be put at absolute rest postoperatively if nothing whatever is given by mouth, despite the continuance of gastroenteric secretion for a brief while. For the first day, gastric lavage with solution of sodium chloride may be necessary to control vomiting of accumulated gastric secretions and regurgitated bile, but when a prolonged healing period of the gastrointestinal tract is imperative, for the ensuing forty-eight to seventy-two hours all fluid should be taken parenterally.

Postoperative distention and gastric dilation must be watched for carefully during the first three or four days. Persistent vomiting and distention are as a rule readily controlled by simple gastric lavage with isotonic saline solution. If continuous gastric suction drainage is instituted, it cannot be too often emphasized that chloride and carbon dioxide determinations are required daily in addition to regulated subcutaneous or intravenous volume for volume restoration of the fluid and electrolytes drawn off. It is recommended that the tubes be clamped every two hours with a view to determining how well the patient can tolerate the early discontinuance of suction drainage. Prostigmine methylsulfate in doses of 1 ampule given immediately preoperatively and thereafter every two or three hours for four to six doses has been used to prevent both postoperative intestinal atony and distention and bladder atony and retention of urine. Another procedure recently advocated for the relief of distention is the inhalation of 95 per cent oxygen for a twelve hour period. The insertion of a rectal tube serves to relieve the gas pains of lower intestinal origin. Enemas, however, are best deferred for four to five days as a rule. Pack substantiated the findings of Puestow that morphine,

prostigmine methylsulfate and physostigmine salicylate stimulate the small bowel but inhibit the action of the large bowel, while pitressin has the reverse effect on intestinal tonus, and pointed out that the indications for their individual use therefore vary, depending on whether relief of upper or lower gut distention is sought. If adynamic ileus supervenes, it may be necessary to resort to spinal anesthesia should other measures fail. Should pitressin induce a late drop in the blood pressure, ephedrine may be needed to counteract this.

*Preoperative Preparation of Circulatory and Blood Systems.*—(*a*) Heart and Blood Vessels: As has been pointed out, operative risk is greater in the presence of the types of organic heart disease commonly found in patients of the cancer age, but these conditions are not of themselves an absolute contraindication, and routine electrocardiographic reading in this age group is of obvious advantage. However, if the patient states that he is free of dyspnea or chest pain on ordinary exertion, it is reasonably certain that the functional capacity of the heart will not be overtaxed by the operation except in the relatively rare situations in which sudden death is precipitated by syphilitic aortitis, aortic stenosis, severe heart block or concurrent coronary thrombosis. Preoperative sedation with barbiturate for several days (narcotizing doses being avoided) to allay apprehension is strongly recommended by Blumgart as well as several preliminary test doses of morphine sulfate to forestall a dangerous synergistic effect of suddenly superimposed barbiturate, morphine and anesthetic. Cardiac decompensation at rest necessarily contraindicates all but extremely urgent surgical procedures of an emergency nature. Although digitalization as a routine supportive measure is to be condemned, since it adds to toxicity when it is of no clinical avail, to correct cardiac failure or combat the presence of auricular fibrillation (the latter in itself is not a contraindication to operation) it should be carried out. When severe hypostatic congestion is found and rapidity in therapy is demanded, the use of strophanthin and mercurial diuretics is indicated. Theophylline with ethylene diamine or one of the related xanthines is indicated in cases of agina pectoris and coronary sclerosis as a useful preoperative adjunct for coronary vasodilation.

Levine reiterated that the well compensated patient with organic heart disease will, in general, stand major operations satisfactorily. It may be briefly mentioned here that although procaine hydrochloride as a local anesthetic is productive of the fewest electrocardiographic irregularities and chloroform, of the most, either is apparently well tolerated if a local anesthetic will not suffice; this is true also of cyclopropane. However, it is a fact to be borne in mind that anesthetic agents, epinephrine or anoxemia may sensitize the arteriosclerotic heart and induce ventricular fibrillation or tachycardia (a complication which should be prepared against by the surgical and anesthetic staffs).

Consideration should be given in all cases of limited cardiac reserve to the prophylactic use of oxygen therapy. During the stage of anesthesia, high oxygen concentrations are essential to prevent the deleterious cardiovascular and hepatic effects of anoxia. Lundy reported that the major contraindication to inducing anesthesia with intravenous sodium pentobarbital is a cardiac lesion associated to any extent with congestive symptoms. Among drugs to be given with extreme care to patients with heart disease Blumgart cited pitressin (used for distention) and epinephrine since their vasoconstrictor action may precipitate angina pectoris and subsequent collapse. Atropine used indiscriminately may lead to runaway tachycardia.

Since operation among patients with cancer and the middle aged and elderly is on the increase, studies to develop optimum operative technics applicable to this class of patients, with special consideration afforded to the problem of avoiding cardiovascular deaths, must be carried out to formulate standards for the best attainable end results.

(*b*) Blood: The fact that most patients with cancer have a degree of anemia sufficient to retard wound healing, predispose to shock or, as was recently demonstrated, facilitate the onset of edema when a solution of sodium chloride is given parenterally, seldom receives the consideration it deserves.

Hemoglobin and red blood cell determinations carried out on 100 consecutive patients admitted to the surgical services of the Brooklyn Cancer Institute revealed the following figures:

Hemoglobin Percentage:

Normal range: 80 to 105 per cent

Reported range: 42 to 91 per cent

Below 50 per cent, 10 per cent of the cases

Below 65 per cent, 65 per cent of the cases

Above 75 per cent, 24 per cent of the cases

As a check on the accuracy of these findings, it may be noted that 90 per cent of hospital workers periodically tested had hemoglobin values above 85 per cent.

Despite the fact that not all our patients seeking hospitalization for various forms of cancer have cancer in an even moderately advanced stage, some degree of anemia is found to be present in almost all. In this connection, recent experimental work emphasizing a correlation between cancer and hemolysis, disturbances of bilirubin and hemoglobin metabolism and anemia is of added interest. Contributory as well to the development of anemia are: the gross or occult hemorrhage of gastrointestinal or genitourinary lesions; a deficiency in the intrinsic hemopoietic factor of Castle (in the presence of achlorhydria); anorexia and consequent iron and other mineral malnutrition frequently seen in all types of

moderately advanced cancer, and decreased intake of other extrinsic hemopoietic ingredients.

Another phase of the problem of anemia in the patient with cancer that requires attention was brought out by Wills and Elliott, who stressed the often overlooked fact that anemia may develop postoperatively in the chronically ill person who presents at initial examination relatively normal hemoglobin and red blood cell values. Presumably the blood loss during the operation cannot be compensated for by the inadequate ferrous stores of the malnourished person who as a rule is afforded a continued lower iron intake over his prolonged convalescent period. The importance of the greater adoption of hemogenic measures in the operative care of the patient becomes manifest. It has become the established rule in our service to attempt to elevate the hemoglobin level of patients to above 70 per cent by means of a hematinic diet in cases in which emergency operations are required in the face of readings of 60 per cent or lower, to administer three or more preoperative transfusions of 500 cc. of whole blood at appropriate intervals and to follow the operation by at least two additional administrations of 0.5 liter of blood. The common practice of giving one transfusion temporarily to bolster up reduced hemic components does not to our mind constitute more than a token acknowledgment of the frequently existing marked depletion of the body's hemopoietic reserves. The formula of Marriott and Kekwick here quoted may prove serviceable in determining the total required volume of blood necessary to correct a given degree of anemia. The blood volume may roughly be expressed as 40 cc. per pound (0.5 Kg.) of body weight.

$$\frac{\text{Percentage of rise of hemoglobin required}}{100} \times \text{Patient's normal blood volume in cubic centimeters}$$

The acute anemia induced by the operative hemorrhage characteristic of radical resection is a strict indication for prompt and relatively rapidly given transfusions of whole blood. Rapid loss of blood in amounts exceeding 30 per cent of the total volume to 1.5 liters may prove fatal, and 40 per cent of the volume lost in producing shock must be immediately restored. Secondary anemia due to hemorrhage from cancerous organs must not be neglected. When for less emergent restorative indications large amounts of blood must be given to elderly patients, the rate of transfusion must not be lost sight of, because, unlike solution of sodium chloride, the added volume does not rapidly leave the vascular system. As reported by Marriott and Kekwick, the amount of blood required for every 10 per cent or 10 mg. increase of hemoglobin in the average adult is about a pint (0.47 liter). When an increase of more than 33 per cent is desired, the transfusion should be done in two stages with an interval of two days between. In the average adult, 1 cc. per pound (0.5 Kg.) per hour is the most rapid rate at which citrated

blood can be given safely. The incidence of untoward reactions increases at faster rates. If cardiac or respiratory disease is present, the amount per hour should be cut in half to prevent pulmonary edema. The only absolute contraindication to transfusion is acute pulmonary edema.

However, in the patient with cancer the presence of nephritis, gastrointestinal or pulmonary hemorrhage, peripheral vascular disease, thrombophlebitis, or embolism calls for extreme judiciousness in the use of whole blood. The febrile reaction seen after transfusions requires no more than symptomatic therapy. The commonest grave complication of blood administration is the hemolytic reaction; this is often accompanied by shock and anuria. These must be watched for, and the merest suggestion of them demands the immediate discontinuance of the transfusion. These reactions are considerably diminished by the use of plasma, untyped and readily stored, which may be used effectively in the treatment both of acute hemorrhage and of shock, as described by recent investigators. Incompatibility, hemolysis, degeneration of stored blood (inhibited by isotonic solution of dextrose), particulate contaminants, pyrogens and an increase of potassium have been described as responsible for transfusion reactions. It appears that such recently advocated blood substitutes as isoagglutinin-neutralized universal blood, cross-matched ascitic fluid, desiccated or spray-dried or frozen plasma, resuspended as a concentrate if so desired, and serum are less productive of such reactions than their precursors.

*Care of the Patient with Jaundice.*—As previously indicated, the recent conclusion of Ravdin that a high protein dietary component equals in importance a high carbohydrate concentration in the protection of the liver has influenced the diets we give before and after operation. When possible, the usual recommendation to defer operation until the serum bilirubin is less than 20 mg. per hundred cubic centimeters should be heeded. However, since icterus of malignant origin is progressive rather than remittent as a rule, it is seldom that it may be taken to apply in cases of cancer. The carbohydrate requirement of approximately 500 Gm. daily cannot be entirely met by the 250 Gm. available in 2,500 cc. of 10 per cent solution of dextrose given intravenously. An additional supplement of 250 Gm. of carbohydrate as well as 100 Gm. of protein must be administered by other routes and, when necessary, by orojejunal feedings. Vitamin concentrates are doubly required since liver disease means impaired hepatic storage of at least vitamins A, B, C, D and K.

Several recent studies confirmed the impression that the newer vitamin K synthetics given in small quantities intravenously may be substituted for the natural derivative formerly administered; 3 mg. of vitamin $K_3$ or an equivalent naphthoquinone is given daily, one dose the day before, and one after the operation. The response, poor in the presence of severe damage to the liver, occurs with a rise in blood pro-

thrombin levels within two hours. Transfusions, at least one preceding and following operation, are continued as heretofore, and in effect augment action of the vitamin K. Bleeding and coagulation times, simpler to obtain than prothrombin determinations in a municipal hospital, although the latter are preferable, are taken twice preoperatively and once postoperatively. Reed found that large amounts of extract of adrenal cortex favor a 30 per cent increase in the coagulation rate of the blood. Apparently this effect obtains even in the presence of cholecystitis and mild icterus. Weir and Coller proposed that ineffective prothrombin response to the administration of vitamin K serves as an indicator of hepatic injury.

The relation of vitamin K deficiency to cancer has of late assumed added interest in view of the experimental work of Fieser, who demonstrated a protective mechanism against methylcholanthrene carcinogenesis in mice associated with the administration of vitamin K and elevation of blood prothrombin. In a small series of blood prothrombin determinations, however, we have failed to find blood prothrombin deficiency a characteristic concomitant of all forms of cancer, although Fieser's observations indicated that possibility. A more complete survey of this matter will be presented at a later date. The fact that prothrombin levels fall rapidly after restoration with vitamin K emphasizes the necessity for prolonged therapy.

*Thrombosis and Embolism.*—Cardiac disease, since it predisposes to congestive heart failure, circulatory insufficiency and venous stasis, and the peripheral vascular diseases frequently met with in the middle aged are responsible for the somewhat increased tendency to thrombosis and embolism seen postoperatively in patients with cancer. These complications, when they occur, are apt to become evident from the fifth to seventh day of convalescence, but grave attacks generally occur on the tenth day, according to Westdahl. When the clinical condition of the patient seems to indicate such measures, particularly in cases in which pelvic operations are to be done, when the risk of thrombosis is known to be greatest or when a second embolus is to be prevented, the use of heparin as a preventive measure may be warranted. This is suitably administered as 30 cc. (60,000 anticoagulant units) of heparin solution added to a liter of venous infusion fluid daily at a flow rate of 25 drops per minute for four to ten days. The clotting time of venous blood should be kept at a level between fifteen and twenty minutes. This obviates the danger of excessive bleeding. Several hours after heparin stoppage, coagulation times become normal. De Takáts discussed the role of hemoconcentration and shock in leading to thrombosis.

Potts and Smith showed an increase in volume of blood flow in the inferior vena cava after deep breathing and leg exercise. Prevention of venous stasis in the lower extremities is the crux of the prevention of

pulmonary embolus. To combat phlebitis when large vessels have been manipulated, patients are urged to move about early in convalescence. Frykholm stated that elevating the head of the bed (Fowler position) for 1 or 2 hours daily encourages lower limb activity and prevents thrombosis. He recommended daily palpation of the sole, the calf and the thigh for tender areas. Westdahl concurred in this viewpoint. It is our impression that the beneficial effects on neurovascular and muscular tone obtained by having the patient active and out of bed, when feasible, for several days prior to operation also serves to prevent thrombosis. That continuous intravenous infusion, particularly when one vein has been used time after time, produces thrombosis in the veins of the upper or lower extremities, as the case may be, is another common experience. Culp pointed out that when thrombosis is suspected routine daily measurements of the leg circumference from the malleoli upward may lead to early recognition and that by enforcing prolonged rest in bed in these instances one may possibly forestall pulmonary embolism. Walters expressed the opinion that thyroxin, by increasing the rate of circulatory flow, is of specific value in the prevention of postoperative pulmonary embolism. It is hardly to be expected that patients with cancer with massive pulmonary emboli after extirpative procedures could be considered as candidates for drastic pulmonary vein operative interventions. Patients surviving this complication long enough to receive any treatment seem to improve somewhat after the use of papaverine in large doses used simultaneously with helium-oxygen therapy. Sears advises ligation of the femoral vein when postoperative thrombophlebitis, often revealed only by persistent pain in the calf, is recognized for the prophylaxis of postoperative pulmonary embolism and for the prevention of recurrence if initial embolization has been survived.

*Respiratory Complications.*—Under the heading of infections, a brief discussion of the prevention and treatment of postoperative pneumonia will be presented. The larger aspects of the problem of postoperative pneumonopathies are probably best considered in relation to the predominantly mechanical phases concerned prior to the onset of actual pneumonitis.

Several recent collective reviews corroborated the generally held impression that atelectasis is the predominant postoperative pulmonary complication. Massive lung collapse represents an extreme and grave phase of this condition, and from it stems also postoperative pneumonia, according to the newer concepts. In cases of postoperative bronchitis, pneumonitis and lung abscess, infection, frequently autogenic, assumes the dominant role over the previously mainly operative mechanical factors. Pulmonary embolism and infarction are more properly categorized as vascular accidents.

People of 50 years of age or over, leading an enforced sedentary existence over a prolonged period and with early cardiac and pulmonary degenerative disease, such as arteriosclerotic heart disease and initial emphysema, have limited vital capacities at best. The added strain of temporary circulatory and respiratory embarrassment attendant on any major anesthetic and surgical procedure leads to some degree of hypostatic congestion and hypoventilation in every patient with cancer during and after the operation. It is precisely these two physiologic disturbances that favor atelectasis and that must be overcome to minimize the incidence of this complication. Hypoventilation is chiefly due to pain and reflex spasm, but it originates also to some degree from the decreased tonus of the muscles and nerves involved in inspiration and expiration which may follow actual operative trauma, as after procedures in the upper part of the abdomen lessening diaphragmatic mobility. Reflex circulatory disturbances of a magnitude to produce some degree of pulmonary stasis is the usual occurrence in major abdominal or thoracic resections, and these coupled with hypoventilation result in relative anoxemia.

The character of the bronchial content requires attention in this regard. The concept of Coryllos and other workers that a thickened inspissated mucous plug effectively obstructs a bronchial or bronchiolar passageway, resulting as air absorption is completed in lobar, segmental or scattered lobular atelectasis, as the case may be, suggests another important avenue for prevention and therapy. These nonfunctional consolidated areas are rapidly invaded by micro-organisms normally found in the upper respiratory passages with the picture shortly becoming that of pneumonitis. Since the temperature may by reflex disturbance be elevated before pneumonia supervenes, fever cannot be accepted as a reliable differential diagnostic sign between pulmonary infection and atelectasis. In general, roentgen evidences of diminished lung aeration during the first thirty-six to forty-eight hours should be interpreted as atelectatic phenomena. Since prompt prophylactic procedures against pneumonia must be instituted, there is little significant difference in therapy between the two at this stage. To return to the matter of bronchial secretions, Gordon suggested the possible harmful effects of the indiscriminate preoperative prescription of atropine to diminish them, holding that bronchial obstruction is favored by the resultant thickened viscid mucus secreted. Numerous observers have stressed the hazards of neglecting the stuporous patient, whose normal cough and other removal mechanisms are suspended for several hours immediately after the operation, when thick nasopharyngeal secretions or aspirated vomitus or blood may accumulate in the tracheobronchial tree. A further reason for routine use of the Trendelenburg position in the unconscious patient is the postural drainage it affords.

All too often the admonitions to change the position of the patient frequently and to avoid excessive narcotization are overlooked by the

busy resident and nursing staff. Feeling that to neglect these precautions is particularly hazardous in our type of patient, detailed instructions for the proper handling of each patient in this regard are given. Hyperventilation is encouraged by carboxygen inhalations, and instructions for deep breathing and periodic coughing exercises are outlined. Although no noncontroversial evidence as to the relative advantage of any of the opium derivatives over morphine in depressing the activity of the respiratory center has been presented to date, the recommendation of Harrington and others to supplement small analgesic dosages of morphine with codeine and barbiturate sedatives or prostigmine synergism is followed. The anesthetist, before returning the patient from the operating room, often clears the airway by thorough bronchial suction via catheter. Bedside chest plates are routinely ordered and in the presence of dyspnea, cyanosis, thoracic pain and fever are repeated at intervals.

Minor degrees of atelectasis, once established, may be treated by vigorous application of the measures already described. The patient is instructed to cough and breathe deeply and is given continued administrations of mixtures of carbon dioxide and oxygen. Vigorous percussion over the affected lobe as the patient in the Trendelenburg position coughs with attempts to expectorate is a manipulation which several times seemed to yield good results when we carried it out. More severe forms of atelectasis respond best to emergency bronchoscopic aspiration of obstructing mucus. Coramine, caffeine, metrazol and similar preparations may be judiciously administered to stimulate respiratory activity and are of especial value in counteracting hypoventilation secondary to the use of large doses of analgesic or sedative medicaments. Care must be taken also to avoid unnecessary constriction of the lower ribs and the abdomen by dressings or restraints. As is obvious, uncontrolled abdominal distention, by increasing the patient's dyspnea, is an important contributory factor in the development of pulmonary disturbances.

Intrathoracic surgical procedures require careful postoperative control of intrapleural pressures. Routine readings are carried out at the close of the operation and checked frequently at the bedside. To obviate the possibility of tension pneumothorax, a tube or a large bore needle introduced intercostally is attached to a water-sealed gravity suction apparatus, as described by several thoracic surgeons. Negative pressures in excess of 20 mm. of mercury are avoided lest intrathoracic hemorrhage and exudate be increased. The advice of Alexander to prevent the paradoxic motion of the thoracic wall by elastic compressive dressings and by having the patient lie on the side operated on is heeded. In this manner thoracic shock associated with cyanosis, rising pulse, shallow breathing and falling blood pressure secondary to the transmission of the paradoxic motion to the mediastinum is rendered less likely.

In all conditions in which respiratory difficulty is anticipated this administration of oxygen to lessen anoxemia is carried out. If acapnia or hypoventilation occur, 6 per cent carboxygen for periodic inhalation is given. Marked dyspnea is, in our experience, seldom completely relieved by the customary tent atmosphere of 60 per cent oxygen. It is our impression that the oxygen tent is best indicated when some form of air conditioning is as important as added oxygenation. Thus, in extremely hot weather, the controllable temperature and humidity of an oxygen tent can be utilized to forestall excessive perspiratory fluid and electrolyte loss. Likewise, the pneumonic patient with hyperthermia may do well in the coolness of the tent. However, it is often lost sight of that the status of patients susceptible to shock may be seriously aggravated by chilling.

The recommendation of the surgeons at the Mayo clinic that 100 per cent oxygen be administered by face mask, when needed, for periods up to forty-eight hours seems to work out well in patients showing marked respiratory difficulty. Their recent studies on mixtures of oxygen and helium, indicating that this lighter than air combination diffuses in the lung alveoli into the blood with a minimum of physical respiratory effort, suggest that the necessary equipment is indispensable in the armamentarium of hospitals seeking to give the best of modern operative care. With mixtures of oxygen and helium at a pressure of 6 mm., in which the former is kept above 20 per cent and the use of a Boothby-Lovelace-Bulbulian mask as described by its originators, sufficient oxygenation to sustain life with little breathing motion on the part of the patient can be maintained. This has proved of considerable clinical value in the treatment of shock and postoperative pulmonary complications, especially pulmonary edema, and seems to be of some worth in the relief of severe abdominal distention.

*Infections (Pneumonia, Peritonitis, Wound Healing).*—As has already been emphasized, the essence of prevention in hypostatic and atelectatic pneumonia depends on combating the more or less mechanical processes responsible. The relative merits of spinal and intravenous anesthetics over those of the inhalation type are not as yet established. It is our practice to choose an anesthetic suited to the requirements of the patient in consultation with the physician anesthetist, whose specialized knowledge and experience in the field insure a more logical choice. A synergistic combination of 1½ grains (0.09 Gm.) of soluble pentobarbital given two hours, and ⅙ grain (0.01 Gm.) of morphine sulfate plus $\frac{1}{200}$ grain (0.03 mg.) of scopolamine hydrobromide one and one-half hours, preoperatively is administered in the average case. Doses are adjustable according to body weight. Cyclopropane (intratracheally, if a closed system is required), spinal procaine-nupercaine mixtures,

intravenous sodium pentothal and local procaine infiltration are the anesthetic agents we most often use, in about the order of frequency listed.

In experimental studies with animals, Pickrell found that during anesthesia and for a variable interval thereafter, the immune functions of the organisms are suspended. The inflammatory response is delayed until the period of effective drug action is over, possibly a matter of four to six hours, during which bacterial invasion is observed to proceed unchecked. During this period, in which the body defenses are at a demonstrably low ebb, the pathogenic micro-organisms of the nasopharynx or the colon may gain sufficient impetus to withstand the inflammatory protective processes once they do get under way. This focuses a new light on the causative modus operandi of postoperative pneumonia and peritonitis and adds another reason for avoiding prolonged periods of anesthesia, particularly in the debilitated or elderly sufferer from cancer. Both before and after operation, rigorous attention to oral and nasopharyngeal hygiene is therefore of importance. If need be, consultation with regard to the dental and the nose and throat condition should be requested. Infected gingival pockets, paranasal sinus discharges and the sordes so commonly seen in dehydrated chronically ill patients may serve as prolific sources of the secondary bacterial invaders of otherwise low pathogenicity that may gain a septic foothold. Chronic bronchitis, bronchiectasis or emphysema, as the case may be, widely prevalent in patients past 50, is deserving in every instance of careful thought. The powers of resistance to bacterial invasion of the patient at the cancer age should in general be considered as in decline, and the comfortable assumption, warranted in general surgical practice, that a youthful vigorous patient may readily check the renewed onslaughts of the microbic residents after the usual operative insults to the body defense mechanisms should never be allowed to color the judgment of the cancer surgeon.

With regard to the prevention of pneumonitis by chemotherapy, we have felt, as have others, that the prophylactic dose should be estimated as equivalent to the therapeutic dose, pending conclusive studies establishing adequate criteria of the preventive dose for human beings. Fuller lately stated, however, that half doses and blood levels for four or five days may be adequate in the prophylaxis of wound infections. Recently, in view of the comparably low toxicity and the fact that sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) has been repeatedly reported as an effective bacteriostatic agent against pneumococcus and Streptococcus haemolyticus as well as staphylococci, we have adopted it for routine use to forestall infection when anticipated. Studies demonstrating its effectiveness against the typhoid colon bacillus, Streptococcus faecalis and enterococci group of organisms have led us to feel that it

may be of value as a prophylactic against peritonitis, genitourinary and wound infection as well as pneumonitis, although the encouraging results in the small group of cases in which we have employed sulfathiazole to date cannot be considered as conclusive evidence in its favor. Soluble preparations, such as sulfathiazole sodium sesquihydrate, may be used intravenously. Blood studies to guard against hemolysis, icterus, anemia and neutropenia and examinations of the urine for hematuria or anuria are carried out routinely. In the event that serious toxic reactions occur, the drug is promptly discontinued, and fluids are forced.

Not infrequently enteroanastomosis contraindicates the oral administration of sulfathiazole, and recourse to other methods, as intraperitoneal deposition of doses of 8 grains (0.52 Gm.), is required. Here the more soluble sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) may be substituted by subcutaneous infusion if required. When a Miller-Abbott or a duodenal tube is being used, the drug may be given by this means. An 0.8 per cent solution in physiologic solution of sodium chloride is administered at the rate of 2 cc. per pound (0.5 Kg.) of body weight every eight hours. Rectal administration as a 1 per cent solution of one to two times the oral dose, regulated by blood readings, is seldom resorted to. With all of these drugs, particularly sulfathiazole, fluids must be forced to prevent the formation of obstructive ureteral crystalline deposits. Sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) in equal doses is possibly less toxic and may be given in the presence of liver or kidney damage.

Peritonitis, according to various workers, may be reduced in incidence by the use of intraperitoneal vaccines, sodium ricinoleate, serum immunotransfusions and other measures, Other than the use of sulfanilamide and its derivatives and radiation therapy, we have had little experience in the use of these methods. Recent reports by such surgeons as Rankin and Graham, who have had extensive unconvincing experience with various plans for peritoneal immunization, seem to arouse doubt as to their worth. Firor's recent work on the use of sulfaguanidine (sulfanilylguanidine), in doses of 0.05 Gm. per kilogram of body weight every eight hours, for a week before and after operation seems promising.

Wound infections, we feel, are kept at a minimum by the general program aimed at restoring the patient to optimum physical condition and rigid asepsis. However, the value of several recent local therapies is sustained in our experience. First dressings are usually made after two or three days. In recognition of the delayed healing powers often dealt with, sutures are removed in from seven to twelve days. Infected wounds, particularly those in which radiation changes are present and further inhibit the healing processes, are packed and dressed, after saline irrigation, with gauze impregnated with zinc peroxide cream as advo-

cated by Meleney, Reicher, Freeman and Sunderland or painted with 2 per cent aqueous gentian violet solutions. Irrigations with azochloramid in a concentration of 1:2,500 in saline solution or dressings with this compound in a concentration of 1:500 in triacetin are frequently used with good results. The paper by Johnson on the value of azochloramid preparations when bacterial contamination leads one to anticipate wound infection and in speeding healing despite the presence of actual wound infection seems to be well founded. Of late we have been using sulfanilamide, sulfapyridine and sulfathiazole, especially the first since it is more soluble, in the form of crystalline powder dusted liberally over the wound surfaces as a local bacteriostatic agent, following the recommendation in several suggestive reports. A 10 per cent solution of sodium sulfate has been advocated for infected wounds by Lyth. Adhesive approximations and gauze packing may prove less shocking than immediate resuture in wound disruptions.

That the patient with diabetes requires careful preoperative preparation is well recognized. The details of such preparation are not within the scope of this paper. However, a recent warning by Eschweiler may well be repeated, namely, that the routine practice of covering 500 cc. infusions of 10 per cent solution of dextrose by 25 units of insulin may precipitate hypoglycemia. Insulin shock is a grave complication in chronic invalids and aged patients. A moderate glycosuria in the absence of ketosis is preferable to the risk of postoperative insulin reactions or coronary thrombosis, precipitated by hypoglycemia, in the elderly. Carbohydrate-insulin balance is left in the hands of the medical service prior to the operation. Immediately before operation and at four hour intervals after operation blood sugar and carbon dioxide determinations should be made. Ordinary insulin is preferable because it is easier to administer than protamine or protamine zinc insulin preparations during this period, and the usual amount may have to be increased because of the relatively high carbohydrate intake given. The procedure of Terry, who recommended 15 units for a red, 10 units for a yellow and 5 units for a green precipitate in four hour urine specimens, increased as required in the presence of acetone bodies, is a suitable routine for postoperative care when blood for chemical analysis cannot be obtained. Normal wound healing may be expected in a nonketotic patient with moderate glycosuria and hyperglycemia. Finally, it should not be lost sight of that ketosis is much more easily forestalled than insulin shock.

## SUMMARY

A review of contemporary advances and an analysis of our experiences with relevant current clinical procedures in the preparation for operation and postoperative care of patients at a municipal cancer hos-

pital are presented. The following factors, of specific significance in surgical procedures for malignant tumors, have been given special consideration:

1. The patient with cancer should in general be considered chronically ill. By the usual standards a relatively poor surgical risk, he is a candidate for radical operation and therefore requires the most diligent supportive preoperative and postoperative care.

2. That some degree of arteriosclerotic heart disease exists is a reasonable assumption in the average patient with cancer. Relative circulatory inefficiency renders congestive heart failure, shock, thrombosis, embolism and hypostatic pneumonia major surgical risks. The routine use of electrocardiography and chest plates is therefore of particular value in the treatment of patients with cancer. Impaired renal and hepatic function, diminished vital capacities, obesity, diabetes, hypertension and vesical retention are likewise frequent concomitants of cancer that must never be overlooked. These require intensive corrective preoperative preparation.

3. Among 100 consecutive unselected patients admitted to the surgical service at Brooklyn Cancer Institute, the total serum proteins averaged below 6.5 mg. in 55 per cent. The carbon dioxide–combining power was found to be under 53 in 58 per cent. The presence of acidosis, ketosis and hypoproteinemia may therefore be considered presumptive in the average patient with cancer. Hypoproteinemia is an index of malnutrition. Malnutrition invariably presupposes the existence of surgical avitaminosis. Hypoproteinemia likewise predisposes to shock, edema and great impairment of wound healing.

4. The average whole blood chloride level on admission to our service was below 450 mg. in 45 per cent of the cases. Particularly in cases of gastrointestinal neoplasm, fluid electrolyte imbalance is a safe general assumption. Except in the presence of electrolyte loss, the routine use of dextrose-saline mixtures will often yield a daily surplus of 20 Gm. of sodium chloride, an amount possibly transcending the excretory function of the kidneys of the middle-aged patients. The clinical rules of Maddock and Coller for water and salt balance have proved satisfactory in our service. Prolonged suction drainage by a Levine or a Miller-Abbott tube, whether or not fluids and salt are given orally, requires volume for volume parenteral administration, since the enteric secretions drawn off are isotonic, while absorption of water and salt appears to take place mainly in the colon. Uncorrected hypoproteinemia, anemia and total base loss have been shown to be associated with little understood disturbances of water and sodium chloride absorption, retention and excretion. A greater incidence of serious surgical problems in water-electrolyte balance may therefore be anticipated in a series of cases of cancer.

5. The real threat of overtaxing the circulation and precipitating pulmonary edema or congestive heart failure must be borne in mind when infusions or transfusions are administered to a middle-aged patient.

6. The patient with cancer has a greater susceptibility to shock because of lowered serum proteins, degenerative changes and anemia as well as the magnitude of the operative procedures. Hematocrit readings and determinations of plasma protein and specific gravity are thus particularly indicated in prevention. Prevention is of paramount importance because advanced shock is generally irreversible. Attempting to combat shock by administration of dextrose-saline solutions is to confuse the problems of shock and fluid-electrolyte balance. Prompt administration of plasma or blood is of greatest avail.

7. Anemia is a well recognized characteristic of patients with cancer but is all too seldom corrected prior to operation. The average hemoglobin content of 65 of the 100 successive patients entering the hospital was below 65 per cent. Uncorrected anemia predisposes to shock, edema and poor wound healing and implies from the outset the handicap of relative tissue anoxia.

8. Postoperative pulmonary complications may be expected to be more common among patients over 50, the age when initial emphysema, coronary sclerosis and chronic bronchitis are commonly seen. Anesthesia and operative procedures must not be unduly prolonged for this reason. Neglect of detailed preventive precautions in this age group may often mean the failure of an otherwise successful procedure.

9. Immediate operation on the patient with cancer without intensive preoperative preparation and postoperative care based on the specific requirements of this group courts an often avertable disastrous end result.

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# ABSORPTION OF SURGICAL GUT (CATGUT)

## I. THE DECLINE IN TENSILE STRENGTH IN THE TISSUES

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The absorbability of surgical gut (newly adopted U. S. P. term to designate sheep intestine prepared for surgical use, instead of the misnomer "catgut") has been a somewhat controversial subject. One of the purposes of this work on absorbability was to ascertain the decline in the tensile strength in the tissues of plain and chromic catgut available from different manufacturers. In 1928, Howes [1] reported his observations on the loss of strength of catgut when embedded in the tissues. The most complete review of earlier studies on catgut was presented by Rhoads, Hottenstein and Hudson [2] in 1937 along with clinical and experimental observations on the decline in the strength of catgut after exposure to living tissues. Further clinical studies on the loss of strength of catgut also were published that same year by one of us (H. P. J.).[3] In 1939, Wolff and Priestley [4] made a comprehensive report on the duration of tensile strength in the tissues of patients for various sizes and types of catgut available from six different manufacturers. In the latter two reports, it was generally found that the behavior of the catgut in the tissues from the standpoint of the duration of tensile strength did not correspond closely with the labels of twenty day chromic or forty day chromic, which were generally in use at that time to designate the "approximate" absorption time of the catgut.

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## METHOD

The decline in tensile strength was studied by a series of 1,500 implants of surgical gut (catgut) in the abdominal muscles of dogs. The standard products of ten companies were subjected to tests. The plain, twenty day or medium hard chromic and the forty day or extra hard chromic catgut from six companies in the various sizes of no. 2 to no. 000 were used. The twenty day, or medium hard, chromic catgut of four other companies was tested in the sizes of nos. 2, 0 and 000. Most of the gut used in these tests was manufactured prior to the change in labeling recommended by the Committee of Revision of the United States Pharmacopeia; hence it will be referred to as catgut. To avoid confusion the following schema represents the new nomenclature and what is presumed to be the equivalent formerly in use.

| | Official U. S. P. Terminology | Terminology Formerly in Use |
|---|---|---|
| Type A: | Plain surgical gut (untreated) | Plain catgut |
| Type B: | Mild chromic surgical gut (mild treatment) | Ten day chromic catgut |
| Type C: | Medium chromic surgical gut (medium treatment) | Twenty day chromic catgut; medium hard chromic catgut, ten to twenty day |
| Type D: | Extra chromic surgical gut (prolonged treatment) | Forty day chromic catgut; extra hard chromic catgut, thirty to forty day |

The operative procedures were carried out on the animals with careful aseptic technic while they were under ether anesthesia. The implants were made with the aid of a long flexible probe at one end of which was an eye through which a 6 inch (15 cm.) length of catgut was threaded. The probe was inserted through a small incision in the upper part of the abdomen into the abdominal muscles and then carried down to the lower part of the abdomen, where a second small incision permitted withdrawal of the probe. When the probe was almost completely withdrawn, the catgut strand was released from the eye of the probe by traction at the upper end of the strand, thus leaving the catgut buried in the muscles. Any excess catgut which extended out through the incision was cut off, and the free ends were replaced deeper in the tissues. The incisions were then closed with fine silk.

Most of the implants were made in duplicate by using a portion of the same strand of catgut in 2 different animals operated on simultaneously. The remaining unused portion of catgut was saved, moistened to permit pliability and then hung up to dry with 30 to 70 Gm. lead weights tied on the end to maintain tension. After thorough drying, the average diameter was determined from several readings with an instrument graduated in thousandths of an inch (0.0025 cm.). A portion of the catgut was used for testing the tensile strength, which is hereinafter mentioned as the original tensile strength. A spring scale graduated to ¼ pound (113 Gm.) was used for these tests. The remaining portion of the catgut strand was saved for digestion tests in enzyme solutions, the results of which will be reported subsequently.

It was usually feasible to implant three to five strands of catgut on each side of the abdomen, depending on the size of the animal. The animals were killed

at the end of various periods, depending on the particular catgut used in the tests. For example, a chromic catgut test might be terminated in 1 animal in seven days, while the duplicate implants in another animal might be permitted to remain for ten days. The plain catgut tests were usually terminated at the end of three, five or, in some instances, seven days. Some of the chromic catgut tests were not terminated until fifteen days. Various combinations of catgut were used in different animals. For example, a certain size of twenty day chromic catgut of six different companies was used in duplicate animals until all sizes had been checked. Then each size of twenty day chromic catgut of one company was matched against each size of the supposedly comparable product of another company. Also, the twenty day chromic catgut of one company was checked against the forty day chromic of the same company. In this way it was possible to have a diversified grouping of the various catguts. In some of the earlier series, the tests were conducted by implanting several different sizes of the same kind of catgut in the same location so that the strands of various sizes were subject to identical amounts of tissue reaction.

After the animal was killed, the abdominal wall was dissected to recover the catgut implants. In some instances, the catgut was in such a state of disintegra-

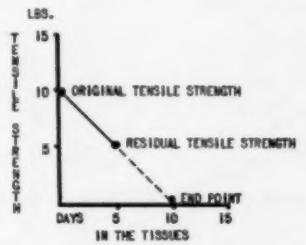


Fig. 1.—Showing graphic method of determining duration of tensile strength of catgut in the tissues.

tion that it could be removed only as fragments or shreds. The intact strands of catgut were removed and hung up to dry. Subsequently a determination of the tensile strength was made, which is referred to hereinafter as the residual tensile strength. Observations were made of the tissue reaction about the various implants. In some series, a specimen of tissue and catgut was taken for microscopic studies. These observations will be discussed in subsequent communications.

In order to make reasonable comparisons of the behavior of different kinds of catgut, it was necessary to express the various observations made in terms of days of duration of tensile strength. Computations of the theoretic end point at which useful holding power is gone can be made either by equation or graph from determinations of the original tensile strength, the residual tensile strength and the number of days the catgut was in the tissues. This is based on the assumption that the decline in tensile strength of catgut in the tissues is a relatively constant factor.

This assumption is supported by work of Howes [1] and of Rhoads and co-workers [2] as well as by observations made during the course of these experiments. For

example, a strand of catgut with an original tensile strength of 10 pounds (4.5 Kg.) may be implanted in a dog for five days. When removed after this period in the tissues, it may be found to have a residual tensile strength of 5 pounds (2.3 Kg.). It has lost 50 per cent of its original tensile strength. This is equivalent to approximately 10 per cent a day. At the end of ten days it would presumably have undergone complete loss of tensile strength. Although the decline in tensile strength of catgut in the tissues may not always be an absolute constant, it is at least sufficiently uniform to afford a reasonable basis for

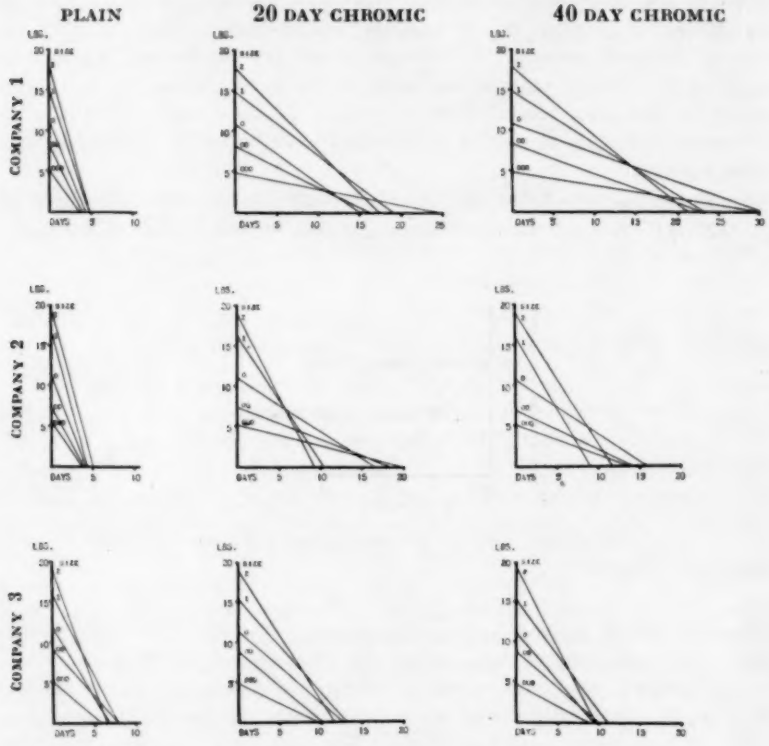


Fig. 2.—Graphs showing decline in tensile strength of catgut in the tissues of dogs (series 1939-1940).

expressing the various observations made in terms of days of duration of tensile strength.

Graphically, the decline in tensile strength can be plotted by drawing a straight line between the points representing original tensile strength and residual tensile strength on the day the catgut was removed. By projecting this downward, it will be found to intercept the base line at the theoretic end point, which represents the expected duration of tensile strength in days. This method is demonstrated in figure 1.

The following equation appears to cover the situation:

$$\frac{\text{T (original tensile strength)}}{\text{T} - t\text{ (original less residual tensile strength)}} \times \text{D (days in the tissues)} = \text{E (theoretic end point)}$$

It is obvious from the aforementioned equation and graph that appreciable errors can be obtained from relatively slight inaccuracies in the determination of the original or the residual tensile strength, especially when the loss of tensile strength is relatively slight over a short period. This source of error was taken into consideration, and calculations which resulted in rather dubious end points were either discarded or corrected.

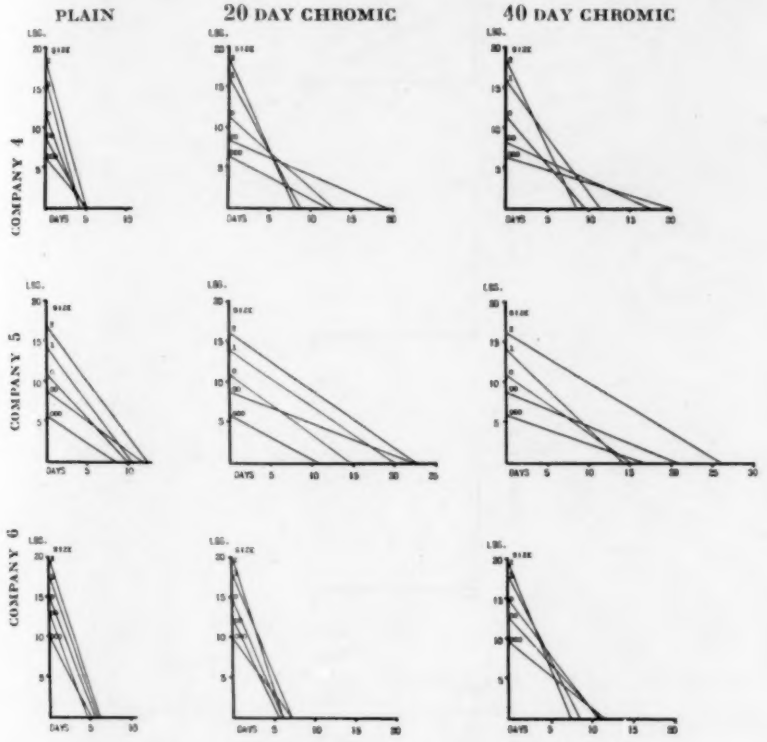


Fig. 3.—Graphs showing decline in tensile strength of catgut in the tissues of dogs (series 1939-1940).

When autopsy revealed that certain strands of catgut were sufficiently disintegrated that only short fragments could be recovered, it was assumed that this represented the end point for this particular catgut. The duration of tensile strength was then computed as the number of days between implantation and autopsy. If the catgut could be recovered only in the form of small shreds, it was considered that the end point had been exceeded by a half day.

After transposing all the observations into terms of days of duration of tensile strength, an average was obtained for each size, kind and brand of catgut. The results are presented in the form of graphs showing the decline in tensile strength

from the average original tensile strength on the day of implantation to the end point when the tensile strength would be negligible on some particular day after implantation.

The first series of graphs (figs. 2, 3 and 4) represents the results obtained from the catgut purchased from ten different manufacturers during 1939-1940.

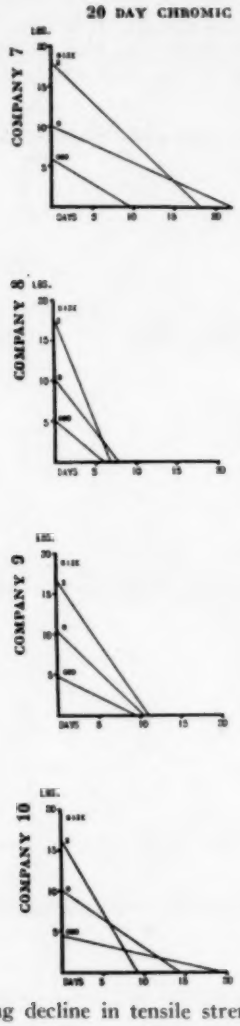


Fig. 4.—Graphs showing decline in tensile strength of catgut in the tissues of dogs (series 1939-1940).

The next group of graphs (figs. 5 and 6) represents observations on catgut obtained for the most part during 1938. The third series of graphs (figs. 7, 8, 9 and 10) compares the results of tests conducted on dogs with clinical tests made on patients. The catgut used for this was acquired to a large extent in 1937,

although some results were incorporated into these charts which were based on catgut obtained prior or subsequent to this date. To avoid confusion the results are grouped into three main series representing approximately the work done during those years.

Regarding the graphs showing the decline in tensile strength of catgut in the laparotomy wounds of patients, the results shown were based on the average duration of tensile strength of each particular catgut as determined by the tension suture test. This was fully described in a previous publication.[3] The end point

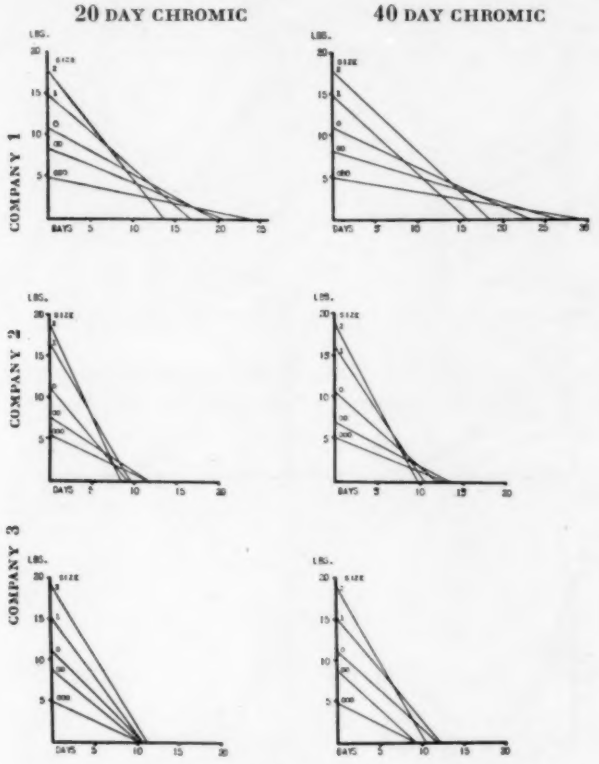


Fig. 5.—Graphs showing decline in tensile strength of catgut in the tissues of dogs (series 1938).

was considered as that day on which the catgut tension suture could be lifted out of the wound with relatively little tension because of practically complete loss of tensile strength of the catgut exposed to the action of the tissues. In instances in which it was desirable to terminate the tests at the end of twelve to fifteen days on certain types of more slowly absorbed catgut, the loop of catgut was cut near the knot which was outside the tissues, and then the strand was lifted out. It was subsequently dried and subjected to a test for residual tensile strength. Then a computation of the theoretic end point was made by either the formula or the graphic method, taking into consideration the original tensile strength and the duration of the catgut in the tissues, as well as the residual strength.

## RESULTS

It can be observed from the three series of graphs that the general behavior of the plain and the chromic catgut of the various companies tested over a period of three years was to a certain extent relatively consistent. On the other hand, appreciable changes in the behavior of some of the brands of chromic catgut did occur.

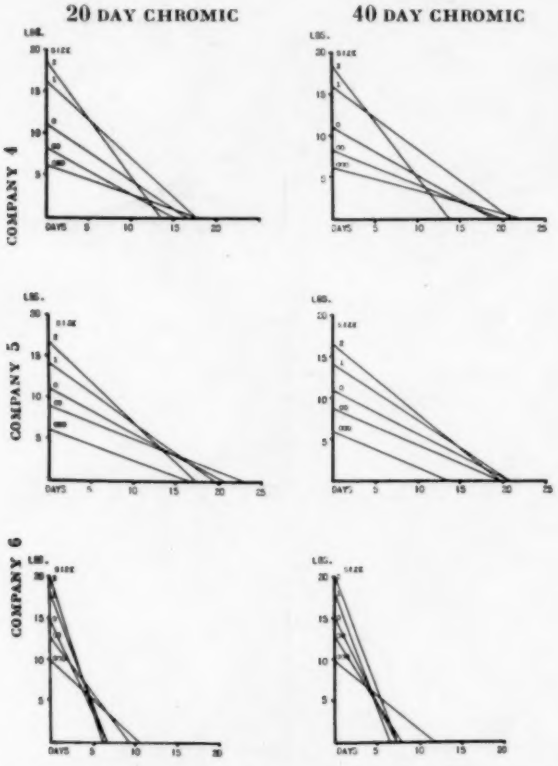


Fig. 6.—Graphs showing decline in tensile strength of catgut in the tissues of dogs (series 1938).

Plain catgut was usually found to undergo complete loss of tensile strength within approximately five days. In a few products, the duration of tensile strength was between five to eight days, and in 1 instance, eight to twelve days.

Chromic catgut showed considerable variation in its performance. In general, it was observed that differences between twenty day and forty day chromic catgut of the same company were relatively slight as compared to the rather striking inconsistencies between the chromic catgut of different manufacturers.

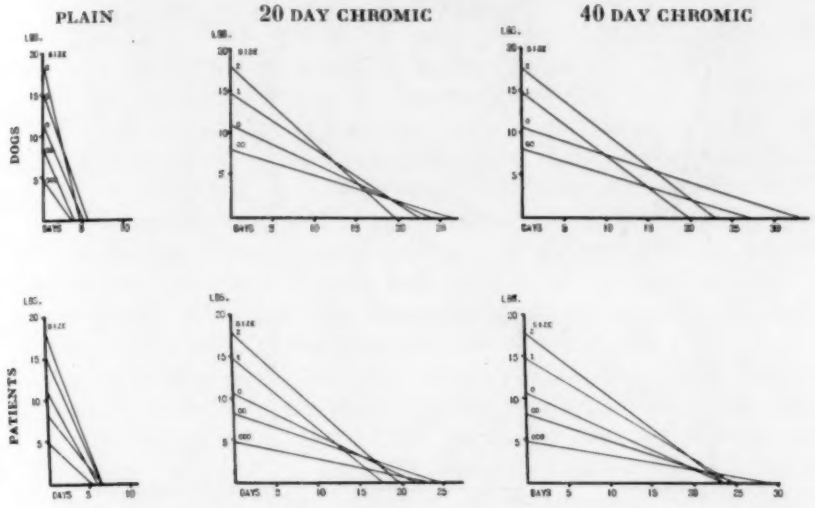


Fig. 7.—Graphs showing decline in tensile strength of catgut in the tissues of dogs as compared with that observed in patients (series 1937; company 1).

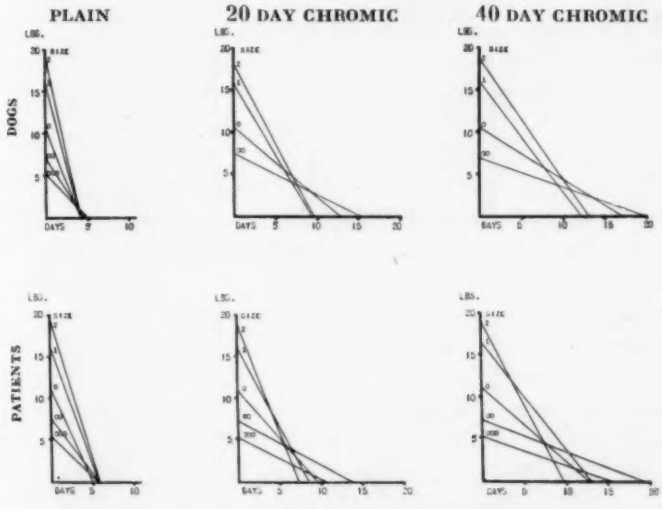


Fig. 8.—Graphs showing decline in tensile strength of catgut in the tissues of dogs as compared with that observed in patients (series 1937; company 2).

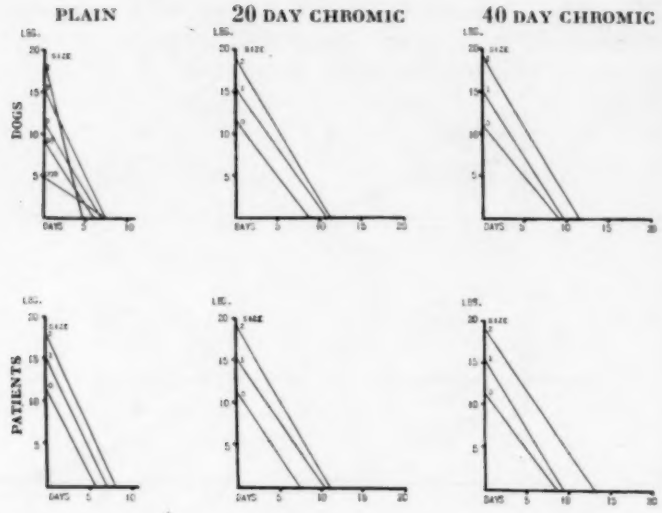


Fig. 9.—Graphs showing decline in tensile strength of catgut in the tissues of dogs as compared with that observed in patients (series 1937; company 3).

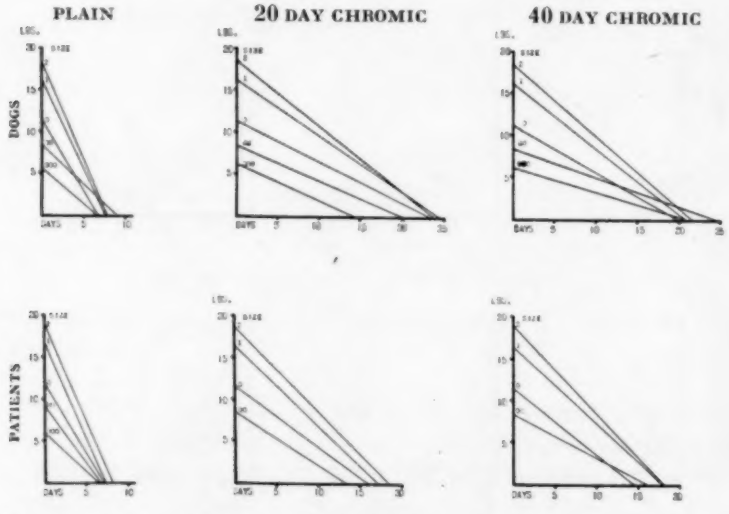


Fig. 10.—Graphs showing decline in tensile strength of catgut in the tissues of dogs as compared with that observed in patients (series 1937; company 4).

The various brands of twenty day or forty day chromic or tanned catgut can be classified only in a general way into three categories: (1) those which did not maintain their tensile strength for a period of ten days; (2) those which held up for ten to fifteen days; (3) those which kept their tensile strength for fifteen to thirty days.

It was frequently difficult to classify a particular type of chromic catgut (i. e., twenty day or forty day) of any one company within the bounds of one of these rather broad categories if the various sizes were taken into consideration. There were numerous instances in which certain sizes performed within the range of one category while other sizes were sufficiently different in behavior to be within the bounds of another category. In fact, some products showed such variation that it was necessary to classify that particular type of catgut in all three categories, depending on the particular size of the catgut.

This phenomenon of difference in behavior of various sizes of chromic catgut of the same company was a rather conspicuous observation in this work. It was frequently observed that the smaller sizes of chromic catgut outlasted the larger sizes from the standpoint of duration of tensile strength. In some products, however, the larger sizes held up better than the smaller. In occasional instances, the duration of tensile strength of different sizes was rather inconsistent, so that no general trend of behavior could be ascertained. It was rather unusual to find a chromic catgut product which had a fairly uniform duration of tensile strength in both large and small sizes. As far as any one product was concerned, the general trend of behavior as related to size was fairly consistent in both the twenty day and the forty day type of catgut.

The graphs showing decline in tensile strength of catgut in the tissues of the dog as compared to the tissues of the patient (fig. 4) were to a considerable extent comparable. In general, the plain catgut was inclined to last about a day longer in patients than in dogs, although the chromic catgut showed a tendency to hold up a few days less in patients than in the animals.

Regarding the individual tests conducted on any particular size, type or brand of catgut, there was a considerable amount of variation in the observations made. This was true to some extent even of duplicate implants from the same strand used in two different animals. A comparison of different sizes, types or brands of catgut could reasonably be made only on the basis of an average of individual tests. At least six to twelve individual results were usually considered in the average which was plotted on the graphs. It should not be overlooked that this average represents an approximate range of behavior rather than a precise evaluation of the duration of tensile strength of any particular catgut.

The calculated end points based on the various individual observations on any particular catgut were usually dispersed in such a way that a considerable proportion of them were within a narrower bracket than

the range between the maximum and the minimum duration of tensile strength. For example, let a catgut which ordinarily averages ten days' duration of tensile strength be considered. The earliest loss of tensile strength in the various tests might be calculated at six days, while the longest duration for this particular catgut might be fourteen days. The maximum-minimum range of variation is therefore eight days. It was usually found that the bulk of the observations indicated a duration of tensile strength between eight and twelve days, which is a bracket of one half of the maximum-minimum range. For catgut which was within the fifteen to thirty day category, the maximum-minimum range was somewhat greater than that observed for the ten to fifteen day classification.

## COMMENT

The rather striking differences in the results obtained with different brands of catgut suggest the need for an improvement in the criterion used by various manufacturers for determining the manner, the method or the extent of treatment, such as chromicizing or tanning, which is used in the preparation of surgical sutures. Further, it appears that the terms used to designate different types of chromic or tanned catgut, such as twenty or forty day, were to a considerable extent misnomers as far as duration of tensile strength in the tissues was concerned. There is little doubt but what the Committee of Revision of the United States Pharmacopeia has taken a justifiable step in the elimination of such terms from the labels of catgut.

Although it has been customary for most general surgeons to use a so-called twenty day chromic catgut for suturing the fascia, especially in abdominal incisions, it appears from these tests that only a minority of surgeons actually used catgut which maintained its tensile strength for a period anywhere near twenty days. An important aspect to consider is what duration of tensile strength has been found by the practical use of catgut to be most desirable for closure of the fascia in the ordinary run of cases of the average general surgeon. Judging from the various products tested, there must be some rather definite reason why the larger sizes of chromic catgut of so many companies do not hold up much beyond ten days. A point to be considered is that if the larger sizes of catgut are chromicized enough to maintain tensile strength for fifteen to twenty days, it is probable that difficulties may arise from this kind of catgut because of the delayed absorption of large bulky knots which may occasionally cause a draining sinus which does not heal until the catgut knot is absorbed or extruded.

The problem of ultimate complete absorption of catgut will be fully discussed in a subsequent paper. It will suffice to say at this time that the complete absorption of chromic catgut after it loses its useful holding power in the tissues is a matter of months if the duration of tensile

strength is beyond ten days. It is believed that the main reason that so much of the chromic catgut in the larger sizes does not hold up beyond ten days is that the manufacturers have found from experience that the tissues do not well tolerate a more thorough chromicizing if so much bulk of suture material is concerned. If a draining sinus develops in a case in which this type of material is used, the surgeon will complain about the catgut. If the manufacturer receives a number of complaints, there is little choice but to make the larger sizes of chromic catgut less resistant to absorption. For the larger sizes of chromic catgut, it is therefore probable that a duration of tensile strength of ten days is about as much as can be expected, in view of the relatively satisfactory clinical results obtained with products which seldom hold up as long as ten days by the tests described. On the other hand, it is possible that improvements in methods of chromicizing may permit a somewhat more resistant suture to be used in the larger sizes without causing an appreciable amount of trouble from draining sinuses in the wounds.

In the smaller sizes, a more thorough chromicizing may be given without causing practical difficulties in the way of draining sinuses, because the lesser bulk of suture material is apparently much better tolerated by the tissues. It is probably because of this that the smaller sizes of chromic catgut of a considerable number of companies showed up better in the tests than the larger sizes. It appears that these companies are attempting to graduate their chromicizing to the relative graded tolerance of the tissues to different sizes of suture material.

It is difficult to understand why there should be appreciable differences in the behavior of various brands of plain catgut and also why a brand of plain catgut might outlast another brand of so-called twenty day or forty day chromic or tanned catgut. There are several sources of supply of the raw catgut available to suture manufacturers. In some instances, the suture manufacturer controls the source of supply. There are probably various methods used in the preparation of the raw product from sheep intestines. If there are appreciable differences in the method of preparation of the raw product before it becomes available to the suture manufacturer, it is not inconceivable that the raw product from one source might differ from that obtained at another source with regard to inherent resistance to absorption. When plain catgut is prepared for surgical use, it is probable that differences in the behavior of different brands of this type of catgut may be due to differences in the methods employed in preparing the raw product.

Further, it is possible that some chromicizing methods may not adequately increase the resistance to absorption of relatively poorly resistant raw catgut to make this outlast plain catgut from another source in which the raw catgut may already possess considerable resistance without additional treatment, such as chromicizing or tanning. Another

factor which may enter into this situation is that the method of preparation of the raw catgut may impart to it certain qualities which in some way tend to negate the effective action of the chromicizing process designed to increase the resistance of the catgut strand to tissue absorption.

The various manufacturers of surgical sutures carry out with considerable precision methods of chromicizing which are designed to render their product as uniform as possible in its behavior in the tissues. Nevertheless, different lots of the finished products sometimes appear to be lacking in uniformity of absorption. This lack of uniformity may be of a magnitude which is appreciably greater than the range of variation of any particular catgut in different test animals. One cannot help but feel that attempts to improve the present variability of catgut behavior in the tissues should be directed at least to some extent toward a more uniform control of the conditions under which the raw produce is prepared.

To the question of whether these tests conducted in dogs are reliable in ascertaining the behavior of catgut in human tissues, the rather striking similarity in the decline in tensile strength shown in the charts (fig. 4) should be an adequate answer. Further, the results of these tests in dogs were to a considerable extent comparable to the observations made by Wolff and Priestley [4] on the duration of tensile strength of catgut in patients. They also observed that some brands of plain catgut outlasted other brands of so-called twenty day chromic catgut. In addition, they drew attention to the greater degree of resistance to absorption of smaller sizes of chromic catgut of some products.

It is probable that the slightly longer duration of tensile strength of the plain catgut in patients as compared to the duration in dogs was due to the fact that some tension was maintained throughout the clinical tests. This delayed the rate of disintegration of the plain catgut, which usually tends to unravel rather conspicuously at the plies when it is placed in tissues without some tension, as was done in the dogs. When catgut unravels freely in the tissues, the phagocytic cells have an opportunity to attack a much greater surface area, and hence the absorption might be expected to be accelerated. The slightly shorter duration of tensile strength of the more resistant type of chromic catgut in patients is probably due to the method of implantation in patients. There may be some reaction in the skin around the catgut at the points at which the catgut comes out through the skin when the tests are carried out longer than ten days. This amount of reaction could cause a slightly more rapid decline in tensile strength of the catgut in the patients. It was rather interesting to observe that the catgut which held up approximately ten days in the patients maintained also its tensile strength in dogs for the same length of time.

## SUMMARY

The decline in tensile strength of plain and chromic or tanned catgut of various sizes produced by different manufacturers has been studied by a series of 1,500 catgut implants in the abdominal muscles of dogs. This survey has included the products of ten companies, some of which have been checked over a period of three or four years.

The rate of decline in tensile strength of catgut in the abdominal muscles of dogs under the conditions prevailing in the tests was reasonably comparable to that observed in the laparotomy wounds of patients when tested by a method previously described as the tension suture test.

Plain catgut was usually found to undergo complete loss of tensile strength within about five or six days, although in some instances the duration of tensile strength was appreciably longer, even extending beyond ten days.

The duration of tensile strength of the various sizes of twenty day and forty day chromic catgut (now labeled type C, medium chromic, and type D, extra chromic, respectively) of the various manufacturers was classified rather broadly into three categories: less than ten days; ten to fifteen days; fifteen to thirty days.

There was a rather noticeable difference in the behavior of the products of the various manufacturers, although only slight differences were observed in comparisons of the twenty day chromic with the forty day chromic catgut of any one company.

The size of the chromic catgut was usually conspicuously related to its behavior in the tissues. In certain products, the smaller sizes outlasted the larger sizes, although in other products the larger sizes held up longer than the smaller sizes. In occasional instances, however, the size of the catgut was not related to any general trend of behavior in the tissues.


## CONCLUSIONS

The implantation technic described offers a satisfactory direct method of evaluating the absorption qualities of surgical gut (catgut) from the standpoint of the rate of decline of its tensile strength in the tissues.

The nomenclature formerly used by many manufacturers to designate the absorption time of their products, such as twenty day and forty day chromic catgut, was sufficiently unrelated to the duration of tensile strength of most products so designated that the discontinuation of this nomenclature is in the best interests of the surgeon as well as of the manufacturer.

It is probable that a duration of tensile strength of about ten to fifteen days may be better suited to the needs of the average general surgeon for routine closure of fascial layers, especially when large sizes of chromic suture material are used.

950 East Fifty-Ninth Street.

# ACUTE APPENDICITIS

## A CLINICAL AND PATHOLOGIC STUDY OF 1,680 CONSECUTIVE CASES

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AND

MENDEL JACOBI, M.D.

BROOKLYN

This paper is a study of 1,680 consecutive unselected cases of acute appendicitis which occurred at the Beth-El Hospital between the years 1930 and 1938, inclusive. The report is based only on cases in which there was pathologic evidence that warranted classification of the condition as acute. No case in which the condition was not diagnosed pathologically as acute is included, regardless of the clinical diagnosis. Parenthetically, it may be noted that during the period under survey there were 194 cases, or 11.6 per cent of the 1,680, in which the patients were admitted with a diagnosis of acute appendicitis which pathologic examination including microscopy failed to confirm.

In evaluating our figures, a brief description of the service is important. The hospital, of some 280 beds, is situated in one of the most congested and densely populated districts in the city of New York (population about 350,000 in about 3 square miles [777 hectares]). This hospital served until recent years almost exclusively the lower middle class or poor patient in this district in the capacity of a voluntary hospital. The average income of a family among its patients was about $1,300 per year; many were on the rolls of various governmental relief agencies. With few exceptions, however, the patients were all literate and frequently were well educated. They were preponderantly Jewish; there were but an occasional Negro and a moderate sprinkling of Italian or Irish patients in this series.

In 59 per cent of the cases here analyzed, the patients were treated as private or semiprivate patients of the various members of the inpatient surgical staff, while in 41 per cent, the patients were treated as ward or free patients by the surgical staff then on service.

It should be stated that the surgical staff and the facilities of the hospital have been substantially the same throughout the period under consideration. It is of importance that all members of the surgical staff beneath the grade of attending surgeon (two men) or associate attend-

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ing surgeon (two men) were supervised in all cases, both before and after operation and during any surgical procedures, by an attending or an associate attending surgeon, regardless of whether the patient was considered a ward, a free or a private patient. All appendixes removed were routinely subjected to careful gross and microscopic examination; in each instance, regardless of the gross findings, sections from the distal, middle and proximal thirds and from the tip beyond the gross lumen were examined. In special cases, additional sections from points of special gross interest were taken.

One further fact is of importance. The people of the district served by the hospital, though in poor financial circumstances as noted before, have, in general, been subjected to a high degree of education by various social and medical groups concerning the dangers of the so-called

TABLE 1.—*Relation Between Preoperative Duration of Symptoms and Mortality Rate*

| Duration of Symptoms | Patients | Percentage of Total | Deaths | Percentage |
|---|---|---|---|---|
| 6 hours | 71 | 4.1 | 0 | 0 |
| 12 hours | 315 | 18.8 | 1 | 0.31 |
| 24 hours | 588 | 35.03 | 8 | 1.3 |
| 48 hours | 326 | 19.4 | 7 | 2.1 |
| 3 days | 152 | 9.09 | 5 | 3.28 |
| 4 days | 86 | 4.4 | 2 | 2.38 |
| 7 days | 91 | 4.7 | 1 | 7.86 |
| 2 weeks | 33 | 1.9 | 2 | 6.06 |
| 3 weeks | 6 | 0.3 | 0 | 0 |
| 4 weeks | 4 | 0.22 | 0 | 0 |
| Over 6 weeks | 8 | 0.46 | 0 | 0 |

bellyache. Physicians, 88 per cent of whom were trained in American or English schools, are easily accessible (416 physicians for 350,000 people) and are likely to be called fairly early to see the patient (table 1 shows that 971 of this series, well over half, were operated on within twenty-four hours of the first symptom, and 1,296, within the first forty-eight hours). Finally, the hospital conducts an active ambulance service of three ambulances, averaging fifty calls per day, and the ambulance surgeons are instructed to hospitalize all patients if there is a suggestion of appendicitis and to prescribe or administer no narcotics or laxatives to patients whose symptoms in any way suggest the presence of an acute condition within the abdomen.

## GENERAL INCIDENCE

During the last eight years, there were 1,680 cases of acute appendicitis substantiated by histologic survey. There were 32 deaths; this represents a total uncorrected mortality rate of 1.9 per cent. In all but

8 cases in this series, operation was done. Pathologic reports of the underlying condition ranged from acute catarrhal to acute gangrenous appendicitis with rupture and generalized peritonitis.

### SEX AND AGE INCIDENCE

In 909 of our cases, the patients were male, and in 771, they were female. Since our general hospital population is about 1.2 male patients to 1 female, it can readily be seen that acute appendicitis is more prone to occur in the male. This is particularly true in children under the age of 12. A study of age incidence shows that the second and the third

TABLE 2.—*Incidence of Acute Appendicitis with Regard to Age, Sex, Signs, Symptoms, Morbidity, Complications and Death*

| | | | | Signs, Symptoms and Laboratory Data | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Sex | | | | | | | | | | | | |
| Age Group, Years | Patients | Male | Female | Abdominal Cramps, With or Without Localization in the Right Lower Quadrant | Nausea | Vomiting | Temperature (100 F. or Higher) | Leukocytosis, With or Without Polynucleosis | Diarrhea, Two or More Watery Stools | Chills | Frequency of Urination and Dysuria | Backache | Morbidity and Complications | Deaths |
| 1-10 | 352 | 195 | 137 | 301 | 275 | 234 | 270 | 268 | 0 | 1 | 5 | 2 | 56 | 12 |
| 11-20 | 613 | 332 | 281 | 604 | 560 | 416 | 491 | 510 | 7 | 6 | 5 | 2 | 55 | 4 |
| 21-30 | 398 | 205 | 193 | 434 | 331 | 228 | 292 | 313 | 2 | 9 | 6 | 1 | 26 | 6 |
| 31-40 | 169 | 97 | 72 | 160 | 130 | 80 | 127 | 135 | 2 | 6 | 6 | 1 | 17 | 4 |
| 41-50 | 88 | 43 | 45 | 73 | 63 | 40 | 61 | 60 | 0 | 6 | 7 | 0 | 5 | 3 |
| 51-60 | 43 | 28 | 15 | 40 | 38 | 29 | 36 | 40 | 0 | 2 | 1 | 0 | 6 | 1 |
| 61-70 | 14 | 8 | 6 | 13 | 11 | 6 | 11 | 11 | 0 | 0 | 0 | 0 | 4 | 2 |
| Over 71 | 3 | 1 | 2 | 2 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 1,680 | 909 | 771 | 1,627 | 1,410 | 1,035 | 1,290 | 1,337 | 11 | 30 | 30 | 6 | 169 | 32 |
| | | | | 97% | 84% | 61% | 77% | 79% | 0.7% | 1.7% | 1.7% | 3.4% | 10% | 1.9% |

decades of life and particularly about the age of 18 in both sexes is the time that the disease most frequently occurs. The youngest patient in our series was 17 months old and the oldest 81 years (table 2). This age distribution corresponds roughly with that of the population of the district.

### CAUSATION

The causative factor in the production of acute appendicitis is still far from being conclusively established.[1] The most generally accepted theory on an anatomic and a physiologic basis is the one which postu-

1. (*a*) Bowers, W. F.: Appendicitis, with Special Reference to Pathogenesis, Bacteriology and Healing, Arch. Surg. **39**:362 (Sept.) 1939. (*b*) Krecke, A.: Ueber die Ursachen und das Wesen des Appendizitis, München. med. Wchnschr. **80**:299, 1933.

lates a constant surge of fecal material high in bacterial content, passing through a long thin organ rich in susceptible lymphoid tissue, in which stasis may occur to a greater or a lesser degree with resultant inflammatory process. This stasis may be aided by mechanical block of fecaliths,[2] foreign bodies or kinks; with interference in the emptying of the appendix, distention results and decreases the resistance of the mucosa and renders this easy prey for the massive amount of organisms already present. It should be noted, however, that in only a small percentage of the cases (14) of our series were there evidences of obstruction by fecaliths, stenosis or external constricting agents; this is in contrast with the high incidence of these conditions found by Wangensteen [2b] and Bowers [1a] and others.[3] In this regard, our findings parallel those of the recent study by Koster and Shapiro [4] as well as the older figures given by Aschoff [5] and Burgess.[6]

In our series, 65 patients, or 3.8 per cent of the entire series, gave a history of preceding infection of the upper part of the respiratory tract. Acute appendicitis may occur by way of the blood stream from the respiratory tract,[7] and when it does occur in this way, it is of a more fulminating character, the process going on to gangrene within a short time. All our patients with an antecedent history of infection of the respiratory tract showed gangrenous appendicitis at operation. All 65 were operated on within forty-eight hours of onset of abdominal symptoms. The antecedent history of infection of the respiratory tract varied from two to six days before the onset of abdominal symptoms. No emboli could be demonstrated in any appendix in this group, nor was there any evidence of obstruction of the organ due to swollen lymphadenoid tissue, as suggested by Bowers,[1a] or of any other obstructive agent. The lymphoid changes in these appendixes were, in common

2. (*a*) Aschoff, L.: Ueber die Bedeutung des Kotsteines in der Aetiologie der Epityphlitis, Med. Klin. **24**:587, 1905. (*b*) Wangensteen, O. H., and Bowers, W. F.: Significance of the Obstructive Factor in the Genesis of Acute Appendicitis, Arch. Surg. **34**:496 (March) 1937.

3. Van Zwalenburg, C.: Relation of Mechanical Distention to the Etiology of Appendicitis, Ann. Surg. **41**:437, 1905. Wilkie, D. P. D.: Acute Appendicitis and Acute Appendicular Obstruction, Brit. M. J. **2**:959, 1914.

4. Koster, H., and Shapiro, A.: Role of Intralumenal Obstruction in Pathogenesis of Acute Appendicitis, Arch. Surg. **41**:1251 (Nov.) 1940.

5. Aschoff, L.: Die Wurmfortsatzentzündung, Jena, Gustav Fischer, 1908; footnote 2 *a*.

6. Burgess, A. H.: A Clinical Lecture on an Analysis of Five Hundred Consecutive Operations for Acute Appendicitis, Brit. M. J. **1**:415, 1912.

7. Adrian, C.: Die Appendicitis als Folge einer Allgemeinerkrankung. Klinisches und Experimentelles, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **7**:407, 1901. Anderson, H. B.: Appendicitis as a Sequel of Tonsillitis, Am. J. M. Sc. **150**:541, 1915. Equen, M.: Appendicitis Following Tonsillectomy: A Clinical Study, Tr. Sect. Laryng., Otol. & Rhin., A. M. A., 1932, p. 130.

with those seen in children generally or in adults in whom the lymphoid follicles were still largely extant, confined to moderate proliferation of the reticulum cells of the secondary follicles, moderate enlargement of these follicles at the expense of the follicle as a whole and the adjacent lymphoid stroma and the presence, in the more severely involved organs, of focal nonspecific necrosis in the secondary follicles, in all respects similar to those seen in secondary lymphoid follicles affected by a variety of generalized infections and exanthems. Careful review of these 65 specimens failed to reveal any occlusion or stenosis or measurable distention of the lumen in any portion of the organ.

Trauma seems to have been the causative factor in 6 cases, or 0.34 per cent of our series. Five of these patients were thin wiry persons belonging to age groups below 20 years.

Fibrocaseous tuberculosis of the appendix with a superimposed acute phlegmonous process was found to be the causative factor in a woman of 33 years, with a typical history of twelve hours' duration of symptoms. The lumen was stenosed proximally by the fibrosing phase of tuberculosis.

Though carcinoid was encountered in 8 cases of this series, the tumor gave no evidence of obstruction pathologically and did not appear clinically to have had any bearing on the development of acute infection. In every instance the neoplasm was an incidental finding.

Our classification of acute appendicitis, as are all morphologic classifications of disease processes essentially dynamic and changing, is admittedly arbitrary. It is of value only as indicating the degree to which the process had advanced when the organ was removed. We believe that by the use of the method of examination of the appendix previously described in brief, a rather comprehensive picture of the process in all parts is obtained. Comparison of the information obtained from these sections with that obtained from longitudinal sections [8] has not convinced us that the latter, somewhat more difficult technically and certainly delaying histologic study (since the organ must first be fixed in toto), yields more exact details. In fact, we have found study of the appendical mural lymphatics and vessels more complete when sections of the entire wall at right angles to the long axis were examined. Further, this method allows the surgeon to be informed of complete pathologic details within twenty-four hours after receipt of the appendix by the laboratory and to guide his further treatment of the case aided by such study. An added objection to longitudinal sectioning is that the necessary preliminary fixation of the organ in toto effectively prevents study of the interior and the wall of the appendix in the natural state.

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8. Bowers.[1a] Wangensteen and Bowers.[2b]

Our department of pathology has throughout the last twelve years looked with considerable disfavor on the pathologic diagnosis of acute catarrhal appendicitis, realizing that at least two of the criteria so often relied on for such a diagnosis—congested vessels and so-called stromal edema—can easily be simulated by the effects of suddenly clamping or ligating the mesoappendix early in the operation or even by mere mechanical handling at the operating table. To make such a pathologic diagnosis, this department has therefore insisted on the presence histologically and in an obvious fully developed manner of all of the following findings:

1. Marked congestion of the mucosal stromal capillaries must be present with a greater proportion of polymorphonuclear leukocytes in the intraluminal blood than in normal circulating blood, i.e., more than 1 to about 500.

2. These leukocytes must be arranged chiefly at the periphery of the vessel, i.e., show the phenomenon of so-called margination, preferably with some evident emigration through the wall.

3. There must be widespread and more or less uniform marked stromal edema.

4. There must be such a marked increase in the polymorphonuclear leukocytes in the stroma—exclusive of eosinophils, which are ordinarily seen in rather large numbers in the mucosal stroma of a noninflamed appendix, especially as a postcibal finding—as to be easily evident under the low power objective of a microscope. Such leukocytes must be rather uniformly distributed.

5. The mucosal glands must be so distended with mucoid secretion that the lining cells show evidence of compression.

With these criteria, there have been only 57 cases in this series (.03 per cent) in which the diagnosis of acute catarrhal appendicitis has been made. Determination of the number of cases of this condition is important in any statistical study since the appendix in this condition is, by definition, more mildly involved. It should be noted that even in these cases there was the added corroborative evidence of inflammation in the presence of distended leukocyte-filled mural lymphatics, vessels not ordinarily seen at all or recognized only doubtfully in the normal organ. This we have chosen to regard as evidence of regional drainage in the same sense as regional lymphangitic drainage in any other infected organ and have termed it appendical lymphangitis. Its significance in appendical inflammation will be discussed in a later communication as well as briefly considered in this paper. In a few instances, chiefly in association with more severe grades of inflammation, we have even seen the lymphangitic process involving mesoappendical vessels.

By acute phlegmonous appendicitis we have designated that picture in which all the layers of the appendix to greater or lesser degree and in widespread or focal manner show evidence of extravascular leukocytic infiltration, with other evidences of inflammation as noted. There is, however, either no or little necrosis of tissue; the mucosa is not ulcerated, and there is no intraluminal purulent exudate, though there may be and frequently is a peritonitic reaction. When mucosal ulceration and pus in the lumen of the appendix (microscopic or grossly frank pus, not tissue juices grossly mistaken for pus) are present, appendicitis is classified as acute suppurative. The term acute gangrenous appendicitis is reserved for organs which show, in the involved portions, a predominance of necrosis of tissue with consequent obliteration of the usual landmarks; perforation need not be present.

We have further included, as a subsection of these classes, the presence of gross fibrosis sufficient to obliterate the lumen. This finding, wherever noted, required microscopic confirmation. Finally, we have noted also the presence of marked leukocytic infiltration of the walls of arteries or veins, with or without thrombosis, as acute arteritis or phlebitis, and the presence of the lymphangitic mural and mesoappendical involvement as given under the description of the catarrhal appendix. These findings were noted in an attempt to obtain information as to whether their presence affects the prognosis or the morbidity in a case.

The finding of localized peritonitis, with or without the formation of abscess, or generalized peritonitis was strictly a gross observation at operation.

### RELATION OF APPENDICITIS TO MORBIDITY AND MORTALITY RATES

Table 3 shows, as was to be expected, no morbidity or mortality associated with the catarrhal appendix. So strikingly uniform are these figures that we were willing, despite our rather severe pathologic criteria, to consider the appendix as not the cause of the clinical syndrome except for the fact that a follow-up study of these comparatively few cases revealed no recurrence of similar symptoms up to two to four years after operation.

When frank suppurative, phlegmonous or gangrenous inflammation occurred, both the morbidity (11.2 per cent) and mortality rates (2.2 per cent) were highest. The added finding of appendical lymphangitis was associated with a rather marked drop in the morbidity (5.9 per cent) and the mortality rate (1.05 per cent). Similarly, the presence of arteritis or phlebitis in association with suppurative or gangrenous disease was again associated with considerable reduction in the morbidity (7.1 per cent) and mortality rates (1.6 per cent) as compared

with the simple suppurative-gangrenous series, though the presence of arteritis or phlebitis is associated with about 1.2 times as great a morbidity rate and 1.6 times as great a mortality rate as the suppurative-gangrenous type showing a lymphangitic picture alone as a pathologic concomitant. These figures suggest that lymphangitis acts as a defense mechanism to prevent the spread of appendical infection and that arteriophlebitis acts in a similar, though less efficient, manner. That lymphangitis may have such a function was experimentally suggested by Menkin [9] and Lurie,[10] who like ourselves, found it not absolute.

TABLE 3.—*Relation of Appendicitis to Morbidity and Mortality Rates*

| Age Group, Yr. | Acute Catarrhal Appendicitis | | | Acute Suppurative Gangrenous Appendicitis | | | Acute Suppurative Gangrenous Appendicitis plus Lymphangitis | | | Acute Suppurative Gangrenous Appendicitis plus Lymphangitis and Arteriophlebitis | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | Morbidity | Mortality | Cases | Morbidity | Mortality | Cases | Morbidity | Mortality | Cases | Morbidity | Mortality |
| 1-10 | 14 | 0 | 0 | 235 | 42 | 8<br>3.4% | 54 | 9 | 2<br>3.6% | 37 | 7 | 2<br>5.4% |
| 11-20 | 25 | 0 | 0 | 406 | 44 | 3<br>0.7% | 109 | 2 | 1<br>0.9% | 72 | 3 | 0 |
| 21-30 | 11 | 0 | 0 | 286 | 21 | 5<br>1.7% | 72 | 2 | 0 | 37 | 1 | 1<br>2.7% |
| 31-40 | 4 | 0 | 0 | 118 | 10 | 4<br>3.4% | 38 | 4 | 0 | 18 | 1 | 0 |
| 41-50 | 3 | 0 | 0 | 67 | 3 | 3<br>4.4% | 10 | 0 | 0 | 7 | 0 | 0 |
| 51-60 | 0 | 0 | 0 | 32 | 6 | 1<br>3.1% | 2 | 0 | 0 | 7 | 0 | 0 |
| 61-70 | 0 | 0 | 0 | 14 | 4 | 2<br>15% | 0 | 0 | 0 | 0 | 0 | 0 |
| Over 70 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 57 | 0 | 0 | 1,169 | 130<br>11.2% | 26<br>2.2% | 285 | 17<br>5.9% | 3<br>1.05% | 178 | 12<br>7.1% | 3<br>1.6% |

## RELATION OF DURATION OF ILLNESS TO MORTALITY

The question of length of illness from the onset of the first symptom and its subsequent effect can be seen in table 1. It will be noted that the death per hundred cases of acute appendicitis is definitely increased with a history of forty-eight hours or longer (40.4 per cent of all cases in this series).

9. Menkin, V.: An Aspect of Inflammation in Relation to Immunity, Arch. Path. **12**:802 (Nov.) 1931; Studies on Inflammation: V. The Mechanism of Fixation by the Inflammatory Reaction, J. Exper. Med. **53**:171, 1931; Dynamics of Inflammation, New York, The Macmillan Company, 1940, pp. 115, 152, 169 et seq., 183 et seq. and 200 et seq.

10. Lurie, M. B.: Role of Extracellular Factors and Local Immunity in the Fixation and Inhibition of Growth of Tubercle Bacilli, J. Exper. Med. **69**:555, 1939.

The absence of death in cases of over three weeks' duration is not significant, there being too few cases (18 in all) in this group. Of these, 6 were cases of walled-off abscess. Ten patients in this group noted their first symptoms suggesting acute appendicitis three weeks or longer before operation, but the symptoms thereafter were of such a character as to suggest recurrent attacks rather than that the inflammation of the organ was continuous from the date of the first symptom. It was, however, practically impossible to assign such cases to a more exact temporal relation than that noted in the table.

### SIGNS, SYMPTOMS AND LABORATORY DATA

In our cases the signs, symptoms and laboratory data agree with similar details so frequently commented on by other authors. The five cardinal signs and symptoms of Murphy were, in our series, by far the most prominent. Whenever laboratory data did not confirm well marked clinical findings, the former were discounted, usually correctly. We have not found that the Arneth or Schilling counts yielded sufficient additional information as compared with the usual differential count to warrant using these more time-consuming and operation-delaying procedures. Variations in the clinical picture have, in our experience, occurred chiefly in the youngest and oldest groups, in both of which greater reliance has been placed on physical findings (including rectal examination) than on symptoms. Of the latter, nausea and vomiting tended to approximate pain in point of frequency of occurrence. The statistical incidence of signs and symptoms is presented in table 2.

Catharsis definitely plays a part in the progress of the underlying pathologic process. Purging was present in the history in an overwhelming majority of cases that had gone on to gangrenous appendicitis with peritonitis. Twenty-eight (87.5 per cent) of the patients who died gave a history of catharsis.

An attempt was made to correlate the pathologic picture found at operation with the signs and symptoms. It was found, however, that, with the exception of the fact that in every one of the 30 cases in which there were chills there was histologic arteritis or phlebitis or both, no such correlation could be made. Parenthetically, it may be noted that in this series chills were not of grave prognostic import as has been suggested by others.[11] Of the 32 patients who died, only 4 gave a history of chills. The other 26 patients giving a history of chills made an uneventful recovery not delayed or complicated in any manner as

11. Royster, H. H.: Appendicitis, New York, D. Appleton and Company, 1927, p. 114. Colp, R.: Thrombophlebitis of Appendicular Origin, S. Clin. North America **19**:443, 1939. Thalhimer, W.: Chills Occurring Early in Appendicitis Before Operation and Their Indication of Operable Stage of Pylephlebitis, Arch. Surg. **8**:658 (March) 1924.

compared with the recovery of the patients without chills. Our findings agree with those of Strauss and Tomarkin.[12]

Similarly, there was no possible correlation in the suppurative-gangrenous series between the character of the pathologic changes and the duration of symptoms. In fact, even perforation was found, in

TABLE 4.—*Postoperative Complications of Acute Appendicitis*

| Complication | | Cases |
|---|---|---|
| Peritonitis | | 41 |
| Generalized (perforation in 27 cases) (at operation) | 33 | |
| Localized (perforation in 6 cases) (at operation) | 8 | |
| Respiratory disease | | 32 |
| Pneumonia | 18 | |
| Infection of the upper part of the respiratory tract (postoperative) | 8 | |
| Collapse of the lung | 3 | |
| Pulmonary embolus | 3 | |
| Residual abscess (postoperative) | | 25 |
| Pelvic | 22 | |
| Interintestinal | 1 | |
| Subphrenic | 2 | |
| Wound infection | | 12 |
| Intestinal obstruction | | 9 |
| Acute mechanical (preoperative) | 5 | |
| Paralytic adynamic ileus (postoperative) | 4 | |
| Acute cardiovascular collapse | | 4 |
| Pyelonephritis (preoperative) | | 4 |
| Diabetes mellitus | | 4 |
| Thrombophlebitis (postoperative, all in the left leg) | | 3 |
| Evisceration | | 3 |
| Operative fistula | | 3 |
| Suppurative pyelophlebitis (postoperative) | | 2 |
| Rheumatic fever | | 2 |
| Otitis media (preoperative) | | 2 |
| Scarlet fever (preoperative) | | 2 |
| Infectious arthritis (preoperative) | | 2 |
| Aseptic meningitis (probably due to spinal meningitis) | | 2 |
| Salpingitis (preoperative concomitant) | | 2 |
| Abdominal cellulitis (postoperative) | | 1 |
| Subcutaneous hematoma (postoperative) | | 1 |
| Coronary thrombosis (postoperative) | | 1 |
| Nondiabetic acidosis (postoperative) | | 1 |
| Pregnancy | | 1 |
| Acute gastric dilatation (postoperative) | | 1 |
| Chickenpox (preoperative) | | 1 |
| Fibromyoma uteri | | 1 |
| Epigastric hernia (preoperative) | | 1 |
| Chronic cystic mastitis | | 1 |
| Hemolytic icterus (preoperative) | | 1 |
| Ureteral calculus (preoperative) | | 1 |

association with a relatively short history of six hours' or less duration of symptoms (72 cases). These facts again emphasize the dangers of delaying operative intervention in the hope of subsidence, except for reasons hereinafter noted.

12. Strauss, A., and Tomarkin, S.: Acute Appendicitis, Surgery **3**:111, 1938.

### POSTOPERATIVE COMPLICATIONS

There were complications or accompanying conditions in 166 cases (9.9 per cent) of our entire series. Complications occurred much more frequently in the younger and older age groups. These cases are classified in table 4.

### MORTALITY

The total mortality rate of the series was 32 of 1,680 patients, or 1.9 per cent (table 3), as compared with a death rate for all cases in the district of 1.1 per cent. Of these, 21 patients were male, and 11 were female. It is interesting to note at this time that not only is acute appendicitis more common in males but that it assumes in them a more

TABLE 5.—*Causes of the Thirty-Two Deaths in the Present Series of 1,680 Cases of Acute Appendicitis*

| Cause of Death | | Cases |
|---|---|---|
| Generalized peritonitis | | 15 |
| Perforated | 11 | |
| Nonperforated | 4 | |
| Intestinal obstruction | | 3 |
| Perforated appendix | 0 | |
| Nonperforated appendix | 3 | |
| Peripheral circulatory collapse | | 2 |
| Bronchopneumonia | | 2 |
| Pulmonary embolus | | 2 |
| Diabetic coma | | 2 |
| Generalized toxemia, nonperitonitic | | 2 |
| Coronary thrombosis | | 1 |
| Suppurative pylephlebitis | | 1 |
| Evisceration | | 1 |
| Acute gastric dilatation | | 1 |

lethal character. Reference to tables 2 and 3 shows that the greatest number of deaths occurred at the extremes of life; this probably was due to the fact that in these cases the condition was less typical, purging was resorted to more often, and consultation with the physician was late. It is also apparent that dangers increase geometrically in cases in which there is a history of over forty-eight hours' duration of the condition and in which the appendix has perforated without localization. In 60 per cent of the cases in which death occurred, or 19, there was a history of duration of forty-eight hours or longer. In each of these there was an advanced process in the appendix with or without perforation. Table 5 summarizes the causes of death.

Table 6 is a summary of the mortality percentage of other large series of cases reported in the literature. Our figure of 1.9 per cent is not altered, even by excluding the cases of acute catarrhal appendicitis as possible errors of diagnosis. Similar correction of other published

studies containing large numbers of catarrhal appendixes substantially raises the recorded mortality rate.

Early in this study we were impressed by the relative frequency with which death of patients operated on at night occurred.[13] Study of the cases of our 32 dead patients showed that 21 (66 per cent) were operated on at night (after 9 p. m.) or in the early morning hours.

TABLE 6.—*Summary of Mortality Rates in Large Series of Cases of Acute Appendicitis Published Since 1931*

| Author | Cases | Mortality Rate, per Cent |
|---|---|---|
| Tasche, L. W., and Spano, J. P.: Ann. Surg. **94**: 800, 1931 | 700 | 3.40 |
| Hjelmman, G.: Acta Soc. med. fenn. duodecim (Ser. B, fasc. 1, art. 2) **17**: 1, 1932; abstracted, J. de chir. **42**: 465, 1933 | 5,287 | 2.67 |
| Keyes, E. L.: Ann. Surg. **99**: 47, 1934 | 1,850 | 3.35 |
| Seifert, E.: Deutsche Ztschr. f. Chir. **244**: 176, 1934 | 1,350 | 6.80 |
| Donaldson, H. H.: Pennsylvania M. J. **38**: 73, 1934 | 2,700 | 4.80 |
| Quain, E. P.: Arch. Surg. **28**: 782 (April) 1934 | 2,000 | 3.25 |
| Wevill, L. B., and Wallace, H. L.: Edinburgh M. J. **41**: 357, 1934 | 8,265 | 4.40 |
| Stanton, E. M.: Surg., Gynec. & Obst. **59**: 738, 1934 | 16,424 | 5.40 |
| Müller, S.: Hospitalstid. (no. 30) **77**: 34, 1934 | 1,087 | 6.00 |
| Cayford, E. H.: Canad. M. A. J. **32**: 259, 1935 | 614 | 3.40 |
| Krech, S.: New York State J. Med. **35**: 248, 1935 | 4,662 | 7.00 |
| Ramsdell, E. G.: New York State J. Med. **35**: 673, 1935 | 1,013 | 2.40 |
| McKenna, H.: Ann. Surg. **104**: 617, 1936 | 1,257 | 5.00 |
| Schullinger, R. N.: Arch. Surg. **32**: 65 (Jan.) 1936 | 2,653 | 5.08 |
| Jensenius, H.: Ugesk. f. læger **98**: 1085, 1936 | 1,592 | 6.85 |
| Loveland, J. E.: Am. J. Surg. **31**: 87, 1936 | 1,275 | 2.80 |
| Rhodes, G. K.; Birnbaum, W., and Brown, M. J.: California & West. Med. **45**: 458, 1936 | 1,000 | 3.60 |
| Leonard, E. D., and Derow, S.: New England J. Med. **214**: 52, 1936 | 1,000 | 6.40 |
| Reid, M. R.; Poer, D. H., and Merrell, P.: J. A. M. A. **106**: 665 (Feb. 29) 1936 | 2,806 | 6.40 |
| Burghardt, M.: M. Times & Long Island M. J. **64**: 181, 1936 | 892 | 3.90 |
| Young, J. R.: South. Surgeon **6**: 131, 1937 | 1,734 | 4.3 |
| Lazzarini, L.: Riforma med. **53**: 123, 1937 | 800 | 12.0 |
| Sperling, L., and Myrick, J. C.: Surgery **1**: 255, 1937 | 518 | 5.6 |
| Davis, J. E.; Muske, P. H.; Mulligan, P. L., and Gutov, J.: J. A. M. A. **108**: 1498 (May 1) 1937 | 10,000 | 3.8 |
| Holder, H. G., and Wells, J. T.: Surg., Gynec. & Obst. **64**: 239, 1937 | 3,526 | 8.2 |
| Sprague, E. W., and others: Surg., Gynec. & Obst. **66**: 166, 1938 | 1,436 | 2.7 |
| Ray, B. S.: New York State J. Med. **38**: 412, 1938 | 886 | 2.14 |
| Strauss, A., and Tomarkin, J.: Surgery **3**: 111, 1938 | 1,325 | 4.3 |
| Morse, L. J., and Rader, M. J.: Ann. Surg. **111**: 213, 1940 | 8,727 | 2.15 |
| Nassau, C. F.; Lorry, R. W., and Pulaski, E. J.: Arch. Surg. **42**: 296 (Feb.) 1941 | 4,650 | 3.2 |
| Jennings, Burger and Jacobi: Present report, 1942 | 1,680 | 1.9 |

These patients were handled, as far as could be determined, in a manner identical with those on whom operation was performed by day and by the same surgeons and nurses, working with better less crowded operating room facilities than by day. It is further of interest that in each case in which death occurred, the operating surgeon was one of the more active men on service. There was no essential difference in

13. In our experience no patient died in the operating room or as a direct result of operation.

the severity of the diasease noted in these patients or in the duration of symptoms as compared with the patients operated on by day. It seems to us that the factor of fatigue on the part of the surgeon and his staff, including nurses, may have some bearing on the fatal outcome of such cases.[14] The further factor of fatigue on the part of the patient operated on during these hours, as well as postcibal activity of the digestive tract, may be of additional importance in this connection. In any event, these figures suggest that it may be advisable, in the absence of signs suggesting spreading peritonitis, to postpone operative intervention until morning and to attempt to provide rest and supportive treatment for the patient and rest to the surgical team until then.

### TREATMENT

Of our 1,680 patients with acute appendicitis, all but 8 were operated on as soon as hospitalized. The latter 8 patients were treated conservatively because of the long clinical history and the clinical evidences of fulminating spreading peritonitis. Of these patients, 1 died. Of the 7 patients who recovered, the stay in the hospital after operation averaged twenty-four days.

The anesthesia used for all patients in this series was of the spinal type except for children under 12 years of age and patients with cardiac or other specific contraindications. In the latter group, numbering 321, cyclopropane or open ether was used. There were no direct anesthetic complications in any case in this series, except possibly in 2 cases of aseptic meningitis, in both of which the patients recovered without residua.

It is our opinion that one of the important factors in the low morbidity, and perhaps in the low mortality, rate in our series was the operative procedure employed. In 1,567 cases, the approach was by the McBurney incision, the length of the incision never exceeding 4 inches (10.2 cm.). The root of the appendix was easily located by palpation of the cecum, and in most cases the appendix was easily mobilized and delivered. The mesoappendix was ligated with no. 2 chromic catgut suture and cut without clamping. The base of the appendix was then rapidly crushed with a clamp and tied, and generally a purse string suture was placed in the serosa of the immediately adjacent cecum. (No cecal abscesses resulted.) The appendix was then removed with a phenolized scalpel after thoroughly protecting the skin edges and structures adjacent to the appendix with gauze, the stump was inverted into the cecum, and the purse string suture tied. No other peritonealizing procedure was employed. No wipes or packs were ever introduced into the peritoneal

14. Dr. David Kershner, attending surgeon on the staff of Beth-El Hospital, called our attention to this factor.

cavity; fluid was drained, when necessary, by suction. Drainage was resorted to only when turbid foul-smelling peritoneal fluid or localized abscess was found; when the latter was observed, the appendix was removed only if it presented itself on opening the abdomen; no attempt to find it was made. In doubtful instances, drains were not used. In all, there were 124 cases in this series in which drainage was done. The drains were not disturbed until they had been loosened by the discharge itself, usually from four to seven days after operation. Thereafter, they were elevated on loosening and removed, as a rule on the following day. The drains used were of the cigaret type. Dextrose and physiologic solution of sodium chloride were used freely, by the subcutaneous or the intravenous route or both, in generous amounts on the suspicion that fluids and electrolytes needed replacement. We did not wait for frank clinical evidences of dehydration. Morphine, to the point of narcotism, was used routinely during the first twenty-four hours after operation and in sedative doses for several days thereafter. We do not believe that this drug was in any way responsible for the intestinal obstruction encountered in a few cases of this series, and we are firmly of the opinion that the total somatic, intestinal and psychic rest so obtained was of considerable importance in obtaining our results. Patients were usually allowed to sit up on the eighth day, to be out of bed on the ninth and were discharged on the tenth day.

We feel that considerable emphasis should be laid on the McBurney approach since the right pararectus approach is still generally utilized to a greater extent than the McBurney except in cases in which the diagnosis of acute appendicitis is so positive before operation that the possibility of error is excluded. We have felt that since the appendix accounts for the preponderance of acute abdominal episodes requiring operation, and since the symtom pattern in the abdomen due to acute appendicitis is fairly distinct, that the McBurney route, allowing for rapid local exploration with the minimum of intraperitoneal disturbance, is both ideal and most practical, and this our surgical staff has routinely employed on suspicion, rather than certainty, that acute appendicitis was present. In those instances in which, on opening the abdomen along the McBurney route, the appendix was thought not to be involved, it was found easy and a matter of but a few moments to close the incision and thereafter through a new paramedian incision, so placed as not to approach intimately the McBurney incision, to explore the abdomen. In rare instances, the new incision was revised from the McBurney incision. In all, there were but 28 patients in this series requiring such treatment. In none of these cases, apparently, was the morbidity affected by the double procedure, and none of the patients died. We prefer this method of approach to that of revising the McBurney incision in cases in which an incorrect diagnosis has been made, since the lower part of

the abdomen, usually uninvolved in such cases, is kept separate from the seat of the disease, and any peritonitic process can more easily be kept local. In 36 cases in this series, in which the diagnosis was not suspected before operation, a pararectus incision was used. In such cases, however, though included in this series on the basis of the disease found, the operation was really considered as an exploratory lararotomy.

With the McBurney approach, the average time of operation in cases not complicated by abscess was twenty minutes from beginning to and including closure of the peritoneum. (The latter was closed separately from the muscles and the skin.) With a little practice it was found possible satisfactorily by palpation to explore the pelvic organs and the lower part of the abdomen through this incision in cases in which an error of diagnosis had been made before closing the incision preparatory to reentering the abdomen for further exploration as described.

We believe, further, that the McBurney approach used so regularly by our surgeons accounts for the low incidence of local wound infections (12 cases), evisceration (3 cases), abdominal cellulitis (1 case), subcutaneous hematoma (1 case) and postoperative fistula (3 cases) as complications in this series (table 4). Parenthetically, it may be noted that, except in the case of the 1 patient with postoperative evisceration (through a pararectus incision), who died (table 4), all complications were completely healed before the patient left the hospital. We have not seen any postoperative hernia in this series in cases followed for two to seven years after operation.

## SUMMARY

A clinicopathologic study of 1,680 consecutive cases of acute appendicitis is presented.

It is pointed out: (1) that in cases in which mural lymphangitis and arteriophlebitis are present as complications the morbidity and mortality rates are lower than in cases in which these complications are absent (these complications are viewed as localizing defense reactions); (2) that the morbidity and mortality rates rise with the increase in the time interval between onset of symptoms and operation; (3) that catharsis is apparently a prominent factor in cases in which death occurs; (4) that preoperative chills are not of serious prognostic import.

It is suggested that the factor of fatigue on the part of the operating room team and the surgeon and on the part of the patient may be important in bringing about the death of the patient. It is suggested that after hospitalization and diagnosis, night operations be avoided in the absence of signs of spreading peritonitis in order to overcome these factors and to adjust the frequently disturbed fluid-electrolyte balance of the patient.

Particular emphasis is laid on the recommendation of the wider use of the McBurney incision, even in cases in which acute appendicitis is not rigidly diagnosed but only suspected. The advantages of such an approach with a secondary incision on recognition of the error in cases in which an erroneous diagnosis has been made are pointed out.

The symptoms, the signs, the laboratory data, the complications and the causes of death in these cases are recorded and analyzed.

The mortality rate in this series, 1.9 per cent, is compared with those of other recorded large series.

The question of causation is briefly discussed.

The rigid criteria for the diagnosis of acute catarrhal appendicitis are given, and it is stressed that these should be followed in evaluating any statistical studies relative to mortality rate of appendicitis.

It is pointed out that fluids and electrolytes should be given freely without waiting for clinical evidences of disturbed balance.

Some of the cases used in this study are included with the permission of members of the surgical staff of Beth-El Hospital. Mr. Morrell Goldberg, record librarian and assistant superintendent, assisted in compiling the data.

# POLYPOSIS OF THE VERMIFORM APPENDIX

## REPORT OF A CASE

S. SANES, M.D.
AND
DANIEL F. PATCHIN, M.D.
BUFFALO

No other intra-abdominal organ receives such routine surgico-pathologic examination as the vermiform appendix. One might wonder, then, whether there could exist any appendical lesions the discovery of which would elicit surprise. Yet, polyposis of the vermiform appendix is so rare that observation of a single example of this condition is taken as justification for the following report.

### REPORT OF CASE

H. P., a 20 year old white handy man, was admitted to the Niagara Falls Memorial Hospital to the service of Dr. Norman J. Eick on Jan. 26, 1940, with the complaints of vomiting and abdominal pain. He was discharged February 17.

The patient had been in good health until 1936. At that time he began to have attacks of vomiting. These occurred once or twice a week. Emesis usually followed half an hour after a meal. Along with vomiting, the patient suffered pain on the left side of the abdomen. At times there was pain in the right lower quadrant.

Before the patient's entry to the hospital, emesis increased in frequency, and abdominal pain became worse.

A detailed familial history contained no relevant data.

*Examination.*—The abdomen was distended. A freely movable tender lemon-sized mass was palpated to the left of the umbilicus. On different occasions the mass shifted in position; it was found on the right side of the abdomen and in the suprapubic region.

*Roentgen Examination.*—The duodenal cap was large and had a defect in the upper border. Just beyond the cap, the duodenum was not well visualized. In six hours the head of the meal reached the hepatic flexure. A little of the meal was still in the stomach and the duodenum. The terminal part of the ileum and the appendix were not visualized. There was pain with tenderness in the ceco-appendical area, which was referred upward. The colon was moderately spastic.

*Laparotomy* (February 5).—Through an upper right rectus incision, adhesions between the duodenum and the transverse part of the colon were released. The first portion of the jejunum was dilated; the wall was thickened. The distal part of the jejunum was collapsed. Located between the dilated and collapsed portions of the jejunum was a freely movable mass which on incision of the bowel

From the Niagara Falls Memorial Hospital.

proved to be a pedunculated polyp. After ligation of the pedicle, the polyp was excised. The appendix was removed because it was enlarged and injected.

*Pathologic Description.*—Macroscopic: The appendix measured 8 cm. in length. The average circumference was 1.1 cm. The serosa was distinctly injected. The wall, 0.15 cm. thick, was opaque. The lumen contained bloody fluid; there was no fecal matter. Originating 0.8 cm. from the proximal end of the appendix was a polyp 3.7 cm. in length and 0.5 cm. in diameter. Its surface was markedly hyperemic and hemorrhagic. Its base obstructed the proximal end of the appendix. The polyp projected toward the distal tip of the organ. Another polyp, which originated 4.1 cm. distal to the point of attachment of the first tumor, measured 1.7 cm. in length and 0.3 cm. in diameter. Its surface also was hemorrhagic. The second polyp pointed toward the proximal end of the appendix. Its base,

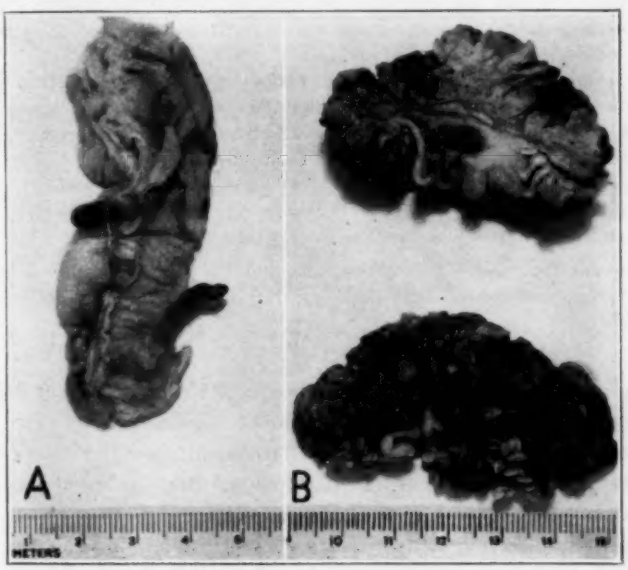


Fig. 1.—Photographs showing gross appearance (*A*) of the appendix with polyps and (*B*) of jejunal papilloma.

0.6 cm. in diameter, appeared sessile and had edges which were firm, immobile and elevated 0.75 cm. above the mucosa. The two polyps overlapped for a distance of 0.4 cm. In their combined length they filled the lumen of the appendix like a cast. Scattered on the appendical mucosa were pinhead-sized opaque elevations (fig. 1).

The specimen from the jejunum was a papillomatous polyp, 7 by 4.5 by 3 cm., attached to a portion of mucosa, 3.2 by 1.3 cm.

Microscopic: In the appendix the largest polyp represented adenoma. It was fairly rich in glands of varying sizes. Some were cystic and dilated; these compressed the adjacent glands and stroma. The lumens of the dilated glands contained fecal material, often in the form of a fecalith. Entrance of feces could be traced to openings in the surface. In some lumens there were red blood cells, neutrophils, eosinophils and mononuclear cells. In most lumens of moderate size, mucus was present. The lining of small and moderate-sized glands consisted

chiefly of a single layer of columnar cells with nearly basal oval vesicular nuclei and with tall mucous borders. Goblet cells were seen. In dilated glands which contained fecaliths, the lining was flattened in places, with hyperchromatic nuclei here and there. In the polyp, as a whole, mitotic figures were rare.

The stroma was slight. It showed edema, infiltration of plasma cells, eosinophils and neutrophils, focal collections of lymphocytes, sometimes as lymph follicles with reactive centers, and swelling of stroma cells. There were extensive recent hemorrhages.

The second polyp also was adenoma. It differed in certain respects from the largest polyp. The glands revealed more marked secretion of mucus, with dilatation of lumen and mucoid degeneration of epithelial cells. The epithelium was inflamed. Interstitial hemorrhage was greater in amount. One vein revealed parietal thrombosis. In a few glands the histologic picture was no longer altogether typical. There was epithelial proliferation within the glands. The nuclei were hyperchromatic. Mitotic figures were relatively numerous. No invasion at the bases of the polyps was seen.

Sections taken from the appendix at various levels disclosed glandular hyperplasia with dilated glands, which contained increased mucus, desquamated cells and neutrophils, in the mucosa. In some places small adenomatous elevations were noted which structurally were similar to the large polyps. The lymphatic tissue varied in amount. The outer layers of the appendix showed no inflammatory infiltration.

Jejunum: The tumor was papillomatous adenoma.

*Postoperative Course.*—The patient developed incisional hernia. He gave a history of the presence of red blood in the stools but refused sigmoidoscopic examination.

## COMMENT

An idea of the rarity of polyposis of the vermiform appendix can be had from the fact that in 1932 Collins [1] compiled only 17 cases from the literature. To these he added what constituted the single instance (an incidental observation at autopsy) encountered in all the appendixes which had been examined up to that time at the Mayo Clinic. In the past nine years, the *Quarterly Cumulative Index Medicus* has listed but 1 report of adenomatous polyp,[2] giving it under the heading of tumor of the appendix. (Cases of adenoma reported by Novis [3] and Satanowsky [4] are excluded because the lesions were not strictly polypous.) Perhaps polyps of the appendix might be discovered more frequently if, when examined, the surgical or autopsy specimen were cut along its entire length.

According to the information tabulated by Collins [1] from the old literature and according to the recent descriptions of Collins [1] and

1. Collins, D. C.: Adenomatous Polyps of the Vermiform Appendix, S. Clin. North America **12**:1063-1067 (Aug.) 1932.

2. Lastra, J.: Pólipo de apendice vermiforme, Arch. de med. inf. **5**:35-39 (Jan.-March) 1936.

3. Novis, A. A.: Tumor apendicular, Bahia méd. **4**:116-118 (June) 1933.

4. Satanowsky, S.: Invaginación crónica del apéndice por adenoma e invaginación recidivante ceco-cólica, Rev. Asoc. méd. argent. **54**:724-727 (April 20) 1940.

Lastra,[2] the available knowledge of polyposis of the vermiform appendix can be briefly summarized. Among the recorded cases, the sex incidence was given as 9 in male patients and 10 in female. In 14 patients, the ages ranged from 6 to 40 years; in 4, from 60 to 80 years. The polypous lesion was situated in the proximal third of 14 appendixes. Three specimens showed involvement of the middle third; 2, of the distal third. The majority of the polyps were small. Measurements ranged from 0.5 to 3 cm. long. Authors attributed symptoms, which varied from six weeks to over a year in duration, to the appendix in 13 cases. Four patients had no symptoms referable to the appendix. Pathologically,

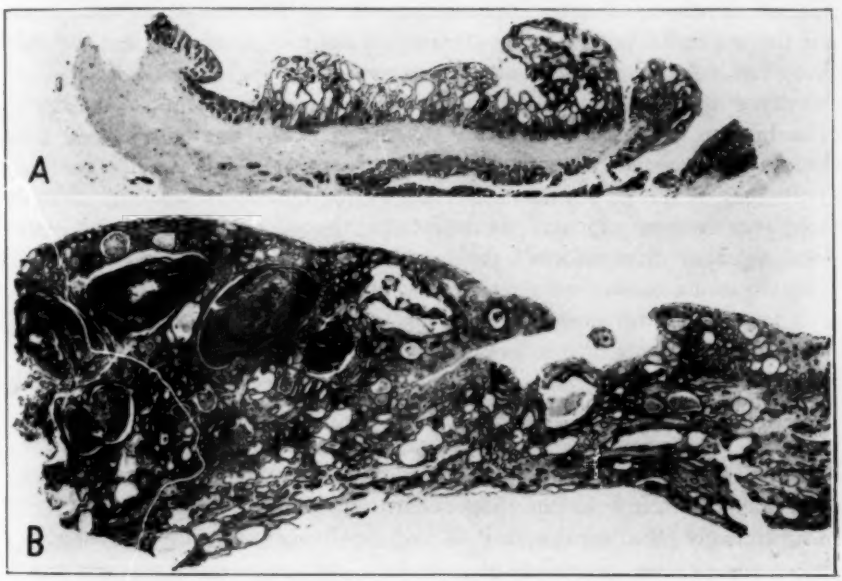


Fig. 2.—Photomicrographs (*A*) of adenomatous hyperplasia of appendical mucosa (× 5⅓) and (*B*) of the largest appendical polyp (× 5⅓).

polyposis was associated with acute, subacute or chronic recurring appendicitis in 10 instances. In 4 cases, intussusception of the appendix and the ileocecal region had occurred. Lastra found oxyuriasis in his specimen.

On the basis of the foregoing summary of the literature, our case bears significance because of certain pathologic characteristics of its own and because of various features of polyposis of the vermiform appendix which it illustrates in general. Ordinarily a single rather small tumor has been described. Of special interest, then, is the gross presence of multiple polyps and adenomas in the appendix which we examined. The largest polyp in our specimen surpasses the maximal measurement

derived from the literature by Collins. Histologically, the findings in our polyps of fecal concretions within glands, venous thrombosis and slight atypical epithelial proliferation are noteworthy.

To the question of the genesis of polyposis of the vermiform appendix, on which there has been speculation in the literature, our case brings two concrete answers. First, development of the large polyps in our specimen can be traced to glandular hyperplasia and adenomatosis of the mucosa. The large polyps are therefore true adenomas. We can exclude their origin on the grounds of inflammation. Whether inspissated feces in glands may act as an irritative factor in mucosa with congenital disposition for adenomatosis is difficult to say.

Of further pathogenic import stands the occurrence of polyposis of the appendix in our patient with polyposis in other segments of the intestine. A large papillomatous adenoma of the jejunum produced obstructive symptoms so that operation was necessary for relief. With the history of melena, polyps were suspected in the rectum and the colon. Pathogenetically, the existence of appendical polyps as part of polyposis of the gastrointestinal tract in the absence of chronic ulcerative enterocolitis supports the neoplastic theory of origin on the basis of congenital disposition of the mucosa. Curiously enough, systematic investigations of the not uncommon condition of polyposis of the colon fail to mention the incidence of involvement of the appendix. In Collins' case there were multiple polyps of the colon with carcinoma of the sigmoid flexure. Recently, Olson [5] demonstrated small adenomatous polyps in the appendix of a 24 year old man who suffered with heredofamilial polyposis of the colon and who died from malignant change in one polyp with metastases. In our case, no heredofamilial history was established through questioning the patient.

Clinically, the implications of the involvement of the appendix in polyposis of the gastrointestinal tract carry practical responsibilities. Before symptoms are completely explained on the basis of polyposis of the appendix, removed through a McBurney incision and, what is more important, before prognosis is made on the sole basis of the appendical lesion (even if the polyps are discovered merely by accident), polyposis of the stomach, the small intestine and the large bowel should be searched for. Witness our case in which polyps were demonstrated in the small intestine and were suspected from the history in the large bowel. Isolated polyposis of the appendix forms the contrasting type.

Preoperative diagnosis of polyposis of the appendix seems impossible. Discovery of this lesion is a laboratory incident. From a speculative standpoint, however, polyps of the appendix might con-

5. Olson, K.: Personal communication to the authors.

ceivably produce pathologic complications and through these, possibly, clinical symptoms. In our case the largest polyp obstructed the proximal portion of the appendix; both polyps filled the appendical lumen, except for its distal part, in castlike manner. In the roentgenograms, the appendix did not fill with barium sulfate. At times our patient complained of pain in the right lower quadrant. The question arises whether polyps of the appendix may cause obstructive symptoms by their size and position. Further, may the obstruction brought about by a polyp act as a determining factor in the genesis of appendicitis? We have already referred to actual cases of intussusception of the appendix and the ileocecal region in which the process was apparently dependent on the peristaltic attempt of the appendix to extrude from its lumen a polyp which represented an obstructing foreign body.

The pathologic specimen in our case suggested how polyposis of the appendix, when it is an isolated lesion and when it does not prevent emptying of the appendical content, may reasonably serve as a rare obscure source of blood in the stool. The content in our appendix consisted of fluid blood. Of course, surgical manipulation brings about hemorrhage into the mucosa and the lumen of the appendix. But appendical polyps themselves, just as polyps of the colon, possess the potentialities for bleeding in erosions of the surface, interstitial hemorrhages, strangulation of pedicle and vascular thrombosis.

Adenomatous polyps of the stomach and colon are notorious for their tendency to become malignant. While carcinoma has not been reported in polyposis of the appendix, it has been assumed that appendical polyps may also undergo malignant change. In one of the polyps in our specimen, glands showed slight signs of atypical epithelial proliferation but no infiltration. On the basis of the possibility of malignant transformation, Collins justified removal of an appendix with polyposis.

76 Butler Avenue.

# NEW DIAGNOSTIC POINTS IN APPENDICITIS

## A CLINICOANATOMIC CONSIDERATION OF BILATERAL HYPERALGESIA

MATTHEW S. LEVITAS, M.D.

BROOKLYN

Evidence of appendicitis has been discovered in mummies of ancient Egypt.[1] The earliest description of the anatomy of the appendix was recorded in 1524 by Jacopo Berengario da Carpi.[2] Vesalius in 1543 termed it the cecum or blind sac. Ambroise Paré in 1582 stated that the intestine has a long and narrow apophysis, but it is believed that Fallopius in 1561 was the first to compare the appendix to a worm.[3] In the nineteenth century renewed interest aroused by the description of Gerlach's valve (1847), Treitz's pericecal fossa (1857) and Clado's ligament (1892) was followed by an active era of clinical, therapeutic and operative progress which is associated with many noted clinicians.

Somatic nerve distribution received early physiologic consideration by Gaskell.[4] He described the origin of the nerves in the spinal segments of animals as having somatic and splanchnic roots. On the basis of clinical observations of various diseases in man, Ross [5] described the regional distribution of somatic and splanchnic pain. Head's [6] classification of various diseases in man on a segmental basis has since received general acceptance. The conception of an overlapping of spinal segments was advanced by Sherrington,[7] Mackenzie [8] and Langley.[9] Mackenzie [8a]

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From the Department of Surgery, Israel-Zion Hospital.

1. Bett, W. R.: A Short History of Some Common Diseases by Divers Authors, London, Oxford University Press, 1934, pp. 162-171.

2. Deaver, J. B.: Appendicitis: Its Diagnosis and Treatment, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1905.

3. Royster, H. A.: Appendicitis, New York, D. Appleton and Company, 1927.

4. Gaskell, W. H.: On the Structure, Distribution and Function of the Nerves Which Innervate the Visceral and Vascular Systems, J. Physiol. **7**:1, 1886.

5. Ross, J.: On the Segmental Distribution of Sensory Disorders, Brain **10**: 333, 1888.

6. Head, H.: A Disturbance of Sensation with Especial Reference to the Pain of Visceral Disease, Brain **16**:1, 1893.

7. Sherrington, C. S.: (*a*) Experiments in the Examination of the Peripheral Distribution of the Fibers of the Posterior Roots of Some Spinal Nerves, Proc. Roy. Soc., London **52**:333, 1892-1893; (*b*) The Integrative Action of the Nervous System, New Haven, Conn., Yale University Press, 1923, p. 254.

8. Mackenzie, J.: (*a*) Associated Pain of Visceral Disease, M. Chron. **16**: 295, 1892; (*b*) The Nature of the Symptoms in Appendicitis, Brit. M. J. **2**:66

*(Footnotes continued on next page)*

proposed the theory that the spinal reflex consists of a visceromotor and a viscerosensory component.

Sensory involvement in appendicitis has been found to extend above and below the level of the distribution of the dorsal eleventh spinal nerve.[8] In July 1903, Mackenzie [8b] stated that the nerve involvement in appendicitis can be grouped within the field supplied by the eleventh and twelfth dorsal and the first and second lumbar nerves. In September 1903, Sherren [10] found a somatic band corresponding to the dorsal eleventh nerve, tenderness often extending to the dorsal tenth and occasionally the dorsal twelfth nerve. He also described a triangular area of sensitiveness in the right lower quadrant of the abdomen. Robinson [11] in 1908 observed cutaneous tenderness of the dorsal eleventh nerve in appendicitis but sometimes of the ninth, tenth and twelfth dorsal and possibly of the dorsal eighth and lumbar first segments. Livingston [12] in 1923 described an appendicular triangle of tenderness extending to the umbilicus.

TABLE 1.—*Maximum Hyperalgesia of Spinal Nerves in Cases of Appendicitis*

| Spinal Nerve | Right Side | Left Side |
|---|---|---|
| Dorsal 11 | 55 | 53 |
| Dorsal 5 | 1 | 1 |
| Lumbar 1 | 1 | 1 |
| Negative | 2 | 4 |

It may be stated that in my experience the dorsal eleventh nerve is mainly concerned in the somatic distribution of hyperalgesia in appendicitis (table 1). This is in accord with the opinion of other observers also.[13] McBurney's point [14] and his description of appendicitis as a

(July 11) 1903; (*c*) Some Points Bearing on the Association of Sensory Disorders and Visceral Disease, Brain **16**:321, 1893; (*d*) Symptoms and Their Interpretation, London, Shaw & Sons, 1909; (*e*) Herpes Zoster and the Limb Plexuses of Nerves, J. Path. & Bact. **1**:332, 1893.

9. Langley, J. N.: Preliminary Account of the Arrangement of the Sympathetic Nervous System, Based Chiefly on Observations upon Pilo-Motor Nerves, Proc. Roy. Soc., London **52**:547, 1892-1893.

10. Sherren, J.: On the Occurrence and Significance of Cutaneous Hyperalgesia in Appendicitis, Lancet **2**:816, 1903.

11. Robinson, H.: The Clinical Bearing of Cutaneous Tenderness on Various Acute Abdominal Disorders, Especially Appendicitis, Quart. J. Med. **1**:387, 1908.

12. Livingston, E. M.: The Skin Signs or Viscerosensory Phenomena in Acute Appendicitis, Arch. Surg. **7**:83 (July) 1923.

13. Head.[6] Mackenzie.[8] Sherren.[10] Robinson.[11]

14. McBurney, C.: Experience with Early Operative Interference in Cases of Disease of the Vermiform Appendix, New York M. J. **50**:678, 1889.

clinical entity have long received the widest clinical acceptance. There are other points of tenderness which lie within close range of the dorsal eleventh spinal nerve, in or near the rectus muscle. Other observers subsequently described such points of tenderness in appendicitis, viz., Lotheissen,[15] Lanz [16] and Clado.[17] Clado's point is located at the intersection of both anterior superior spinous processes and the lateral border of the right rectus muscle. Lanz's point is similar to this except that it is located where the right and middle thirds of the interspinous line join. Morris' point [18] is somewhat higher up. Gray [19] mentioned a left-sided point which is about 1½ inches (3.75 cm.) below and to the left of the umbilicus and which he stated corresponds to the emergence of the terminal branches of the dorsal eleventh nerve. Deaver [2] stressed the importance of Clado's point on the basis of personal observations.

Mertens [20] compared McBurney's and Lanz's point in 309 patients with the following results: 27 were tender at McBurney's point only; 88, at both, and 194, at the Lanz point only.

Deep hyperalgesia has been recognized as a clinical sign. The causal relation has been regarded as a pressure on nerve twigs. Small branches of the eleventh and twelfth nerves pierce the rectus muscle, and tenderness is elicited by pressure on these nerve twigs.[8]

Bilaterality of hyperalgesia has been mentioned by various observers, viz., Head, Mackenzie, Sherren and Gray.[19] They stated that a reflex on the contralateral side may be present in appendicitis. Mackenzie found it difficult to conceive of the appendicular reflex as being unilateral.

Paravertebral block for diagnostic purposes has been used by other observers and myself. They are mentioned by Hewer.[21] Nerve block has abolished pain in gallbladder disease without any effect on pain from adjacent viscera (Rosenthal). It has also been used for acute pancreatitis (Popper) and for angina pectoris (Mandl).

The present study is based on the observation of tender points in appendicitis and the distribution of hyperalgesia above and below the

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15. Lotheissen, cited by Whipple, A. O., in Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1928, vol. 5, p. 315.

16. Lanz: Der McBurney'sche Punkt, Zentralbl. f. Chir. **1**:185, 1908.

17. Clado: Appendice caecal, Compt. rend. Soc. de biol. **44**:133, 1892.

18. Morris, R. T.: Metaplasia of the Appendix Vermiformis and a New Diagnostic Point, New York M. J. **87**:1060, 1908.

19. Gray, H.: Physical Factors in the Production of Appendicitis. Points in Diagnosis: Their Influence on Surgical Treatment, Illinois M. J. **48**:36, 1925.

20. Mertens, V. E.: Der Lanzsche Punkt und seine Bedeutung für die Erkennung des Wurmfortsatzes als Gesundheitsstöres, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33**:557, 1921; cited by Royster.[3]

21. Hewer, C. L.: Recent Advances in Anaesthesia and Analgesia, ed. 3, Philadelphia, The Blakiston Company, 1939, p. 165.

dorsal eleventh nerve. In addition, a detailed study has been made of bilateral tender areas. Paravertebral injection as a diagnostic aid has been utilized in blocking out the several symptoms and signs in appendicitis. This work is a continuation of a previous study dealing with the clinicoanatomic findings in diseases of the urogenital tract.

The clinical study consisted of 60 consecutive cases of appendicitis from the surgical service of the Israel-Zion Hospital and also my private cases and those of my associates. Many additional cases subsequently examined are not included in this series, although they are confirmatory of the results, hereinafter to be recorded. Acute appendicitis with a tense or rigid abdomen has been obviously omitted. These cases are classified as follows: 37 cases of chronic appendicitis, 14 of acute, 4 of subacute, 3 of appendicular abscess and 2 of subsiding appendicitis. There were 38 female and 22 male patients. In 49 cases, the age incidence was from 10 to 30 years. Appendectomy was performed in 55 cases and incision and drainage in 3 cases.

Six of the patients had gangrenous appendicitis; 2 out of 5 patients with retrocecal appendicitis complained of urinary symptoms, and 4 patients had associated ovarian disease—either one condition or the other being primary. The diagnosis of appendicitis was based on the operative findings as recorded by the surgeon. The gross and microscopic pathologic reports (made by Dr. J. M. Ravid, the pathologist of the Israel-Zion Hospital) were used for confirmation of diagnosis.

## ANATOMY OF THE ABDOMINAL WALL

The fleshy part of the external oblique muscle can usually be felt in the lateral abdominal wall as a rounded edge by rolling it under the examining fingers. The interval between the fleshy edge and the lateral border of the rectus abdominis muscle, for convenience, has been termed the fascial space. It is the aponeurosis of the external oblique muscle.

On leaving the thorax between the eleventh and twelfth ribs, the dorsal eleventh nerve lies between the transversus and obliquus internus muscles. At this point in the lateral abdominal wall, the termination of the twelfth or floating rib exposes the dorsal eleventh nerve, making it more accessible to the pressure of the examining fingers. It crosses under the fleshy margin of the external oblique muscle about on a level with the umbilicus. Then it courses obliquely downward to pierce the rectus abdominis muscle at the edge or slightly mesial to its lateral border and on its deeper aspect, about on a line with the anterior superior spine of the ilium. The dorsal eleventh nerve eventually reaches the anterior abdominal wall and becomes cutaneous by piercing the rectus muscle.[22]

22. Cunningham, D. J.: Text-Book of Anatomy, edited by A. Robinson, ed. 5, New York, William Wood & Company, 1928, p. 746.

### RELATION OF TENDER POINTS TO NERVE DISTRIBUTION

In palpation of the tender points observed in appendicitis, I elicited deep hyperalgesia instead of the lighter tactile method used by Head, Mackenzie and Sherren or the vigorous twisting pinch of Livingston.

Pressure pain is a form of deep sensibility. It can be elicited normally by applying pressure over nerve trunks.[23] The various spots palpated bilaterally were: first, at the tip of the twelfth rib; second, at the mesial edge of the fleshy part of the external oblique muscle about on a level with the umbilicus, and, third, somewhat mesial to the lateral margin of the rectus muscle on a level with the anterior superior spine of the ilium (illustration). These spots were tender to palpation and were found to correspond to the underlying dorsal eleventh spinal nerves.

### FINDINGS

*Tender Points.*—The six points of bilateral tenderness just enumerated may be further described as follows (illustration):

Right Side: 1. The first point is in the eleventh intercostal space and is elicited by pressure of the examining fingers at the tip of the twelfth rib.

2. The second point is slightly mesial to the lateral margin of the rectus abdominis muscle about on a level with the anterior superior spine of the ilium.

3. If a line is drawn between the first and second points, the intersection of this line by the mesial margin of the fleshy part of the external oblique muscle represents the third point. This is frequently located on a level with the umbilicus.

Left Side: There are three analogous points on the left side, making a total of six.

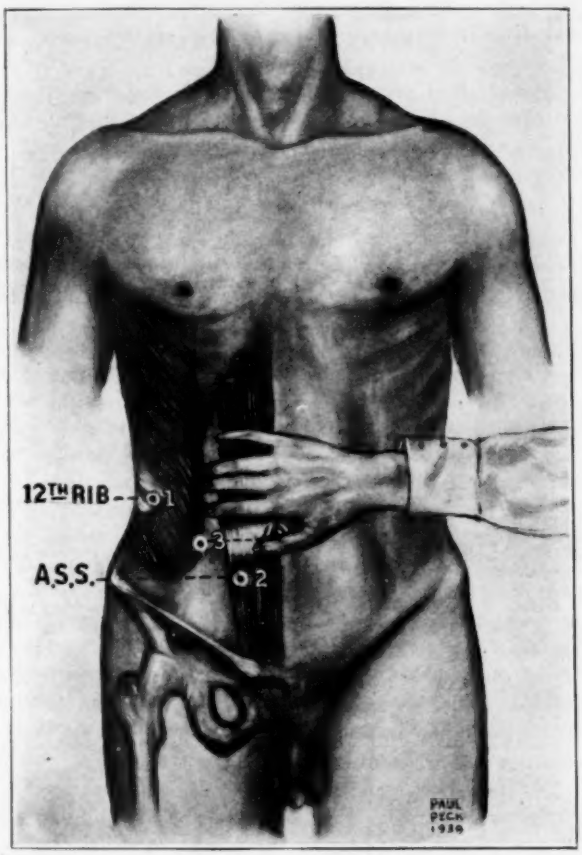
These six points vary also in the comparative degree of individual sensitivity in a given case. The second point, or the one in the body of the rectus muscle, usually evidenced the maximum degree of hyperalgesia. The fascial space was least tender.

*Bilaterality.*—The contralateral reflex was observed in 95 per cent of the cases proved to be cases of appendicitis. This percentage may appear high. Yet, it was obvious that three different points of tenderness were present on the left side. In all instances of bilaterality in this series, contralateral tenderness of the three points was noted in the majority of cases, less frequently two points and but rarely one point.

It may be generally stated that on the contralateral side a lesser number of nerves was involved and that the reaction was less intense

23. Bing, R.: Compendium of Regional Diagnosis in Lesions of the Brain and Spinal Cord, translated and edited by W. Haymaker, ed. 11, St. Louis, C. V. Mosby Company, 1940, p. 30.

than on the homolateral side. In case 33 (table 4), on the right side the involvement extended from the dorsal fifth to the lumbar second nerve, while on the left side it extended from the dorsal tenth to the lumbar second nerve, ten nerves being affected on the right side and six on the left. The comparative reaction of the dorsal eleventh nerve was 2 plus [24] on the right side and 1 plus on the left. The maximum




Points of tenderness (*1*, *2* and *3*) in appendicitis. *A. S. S.*, anterior superior spine of the ilium.

reaction, bilaterally, was noted in the dorsal eleventh nerve as compared with all other spinal nerves involved.

*Paravertebral Injection* (table 2).—The blocking in the region of the right dorsal eleventh nerve afforded an opportunity for studying its

24. One plus indicates slight hyperalgesia; 2 plus, moderate, and 3 plus, maximum.

effect on the various tender spots, hereinafter recorded, in a recognized case of appendicitis. The additional subsidence or disappearance of associated symptoms also was noted.

## REPORT OF A CASE

H. T., a young man 18 years of age, was admitted to the Israel-Zion Hospital on July 22, 1937. Two days before admission, the patient experienced intense pain in the right upper part of the abdomen which gradually localized in the right lower part. He was free from pain for a period of several hours, when another

TABLE 2.—*Somatic Hyperalgesia * Before and After Paravertebral Injection of 5 cc. of a 2 per Cent Solution of Procaine Hydrochloride into the Right Dorsal Eleventh Nerve*

| | Right Side | | | | Left Side | | | |
|---|---|---|---|---|---|---|---|---|
| Location | Before Paravertebral Injection | After Paravertebral Injection (25 Min.) | Before Operation | After Operation (11 Days) | Before Paravertebral Injection | After Paravertebral Injection (25 Min.) | Before Operation | After Operation (11 Days) |
| Dorsal 1 to 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dorsal 7 | + — | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dorsal 8 | + — | — + | + — | 0 | + — | 0 | 0 | 0 |
| Dorsal 9 | + — | — + | + — | 0 | + — | 0 | 0 | 0 |
| Dorsal 10 | + — | 0 | 0 | 0 | + — | 0 | 0 | 0 |
| Dorsal 11 | 1+ | 0 | 0 | 0 | + — | 0 | 0 | 0 |
| Dorsal 12 | + — | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lumbar 1 | + — | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lumbar 2 | + — | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| First point: Eleventh intercostal space at tip of the twelfth rib | 1+ | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Second point: Rectus abdominis muscle slightly mesial to the lateral margin and about on a level with the anterior superior spine of the ilium | 1+ | 0 | + — | — + | + — | 0 | + — | — + |
| Third point: Edge of the external oblique muscle | 1+ | 0 | + — | — + | + — | 0 | + — | — + |

* + — signifies very mild hyperalgesia; — +, doubtful or inconstant.

attack was precipitated after playing a game of handball while at work. During his subsequent twenty-four hour stay in the hospital, the pain recurred, starting in the right lower part of the abdomen and radiating to the upper part of the abdomen. He also felt a soreness in the lower right part of the chest posteriorly. Nausea but no vomiting was present. On examination there was more marked spasm of the rectus muscle and tenderness in the right lower part of the abdomen than in the upper. Tenderness of the dorsal seventh to the lumbar second spinal nerves on the right side and of a lesser number of nerves on the left side and of the six points previously described was observed. The maximal tenderness was noted in the dorsal eleventh nerve.

On July 23 at 11:40 a. m., the patient received a paravertebral injection of 5 cc. of 2 per cent solution of procaine hydrochloride in the region of the right dorsal eleventh spinal nerve.

At 11:45 a. m., the patient experienced no pain in the abdomen or the back and no soreness of the lower part of the chest. On deep breathing, however, he felt a slight pain in the back.

At 12 noon, pain had disappeared in all regions, including the epigastrium, the hypogastrium, the chest and the back.

At 12:05 p. m., no tenderness over the upper rectus muscle or the abdomen was elicited bilaterally. All pain had disappeared anteriorly and posteriorly.

At 12:15 p. m., no tenderness along the entire right or left rectus muscle was present. The rectus muscle was in a state of relaxation although it had been spastic before the paravertebral injection.

At 12:45 p. m., the patient felt some soreness in the right lower part of the chest and the right epigastrium but no pain in the right or the left lower part of the abdomen. There was no soreness felt posteriorly.

At 1 p. m., moderate soreness was perceived in the right upper part of the abdomen and to a lesser degree in the lower part of the abdomen. The pains in the left lower portion of the abdomen also were returning.

On July 24, prior to operation and the day subsequent to the paravertebral injection, pain in the back, the lower part of the chest and the abdomen as well as nausea was gone. There was occasional pain in the right lower part of the abdomen.

On July 24, appendectomy was performed. The appendix was 2 inches (5 cm.) long and retrocecal. The mesoappendix was short. A moderately thickened membrane covered the distal ¾ inch (1.88 cm.) of the appendix, fixing the appendix to the cecum. As a result of this constriction band, there was a pressure atrophy of the distal part of the appendix, diminishing the caliber and the lumen of the appendix. The pathologist reported that there was moderate injection of the serosal vessels, and on microscopic examination the wall was found to be atrophic and to contain dense fibrous connective tissue. The appendix contained two soft fecoliths. Pathologic diagnosis was atrophic appendicitis.

On the day following paravertebral injection and prior to operation (table 2), the patient who had received a paravertebral block presented fewer and considerably less tender nerves and also an amelioration of symptoms. Eleven days after appendectomy, all spinal nerve tenderness, bilaterally, had disappeared except the latter two of the three diagnostic points, which remained barely sensitive to pressure. It is obvious that nerve tenderness had almost completely disappeared.

## ANALYSIS OF THE APPENDICULAR REFLEX

In 6 patients, or 10 per cent of the 60 cases, involvement of the dorsal eleventh nerve only, unilaterally or bilaterally, was noted. No other spinal nerve was affected. Hyperalgesia of the dorsal eleventh nerve alone may therefore be considered to represent, I believe, a pure appendicular reflex, which I have termed a minimal reflex and which may occur unilaterally or bilaterally. The reflex in the remaining 90 per cent of the cases was bilateral, involving more than one nerve and termed a maximal reflex.

The comparative degree of hyperalgesia in the spinal nerves was noted bilaterally. A maximal reaction in the eleventh dorsal nerve as

compared with the other spinal nerves occurred on the right side in 55 cases, 91.7 per cent (table 1), and on the left side in 53 cases, 88.3 per cent.

### THE UPPER AND LOWER LIMITS OF HYPERALGESIA IN APPENDICITIS

A study of the upper limits of bilateral hyperalgesia has been recorded in each individual case in this series (table 3 A). In table 3 B, the lower limits are shown. Comparison of the two parts of the table reveals a more extensive distribution on the right than on the left side, above and below the dorsal eleventh nerve. In addition, on the left side the nerves were considerably less tender.

Analysis of table 3 reveals the extension of hyperalgesia to the upper dorsal segments. This would appear to be a wider diffusion than is

TABLE 3.—*Upper and Lower Limits of Hyperalgesia of Spinal Nerves Above and Below the Dorsal Eleventh Nerve*

| A. Upper Limits | | | B. Lower Limits | | |
|---|---|---|---|---|---|
| Spinal Nerve | Right side | Left Side | Spinal Nerve | Right Side | Left Side |
| Dorsal 3 | 1 | | Dorsal 11 | 22 | 31 |
| Dorsal 4 | 1 | | Dorsal 12 | 15 | 11 |
| Dorsal 5 | 6 | 1 | Lumbar 1 | 10 | 5 |
| Dorsal 6 | 3 | 1 | Lumbar 2 | 10 | 7 |
| Dorsal 7 | 1 | 0 | | | |
| Dorsal 8 | 4 | 0 | | | |
| Dorsal 9 | 7 | 6 | | | |
| Dorsal 10 | 20 | 14 | | | |
| Dorsal 11 | 15 | 31 | | | |
| Total | 58 | 53 | Total | 57 | 54 |

generally reported in cases of appendicitis. However, the clinical picture in this series of cases included the classic symptoms and signs, and the pathologic findings were corroborative. Follow-up observations were not possible in all instances. Whether coexisting conditions other than appendicitis are to be considered in the cases of extreme distribution of hyperalgesia merits further study.

These observations, aided by paravertebral block and postoperative disappearance of the previously enumerated tender spots and disseminated hyperalgesia and associated symptoms, strongly suggest the intimate relation of hyperalgesia as hereinbefore classified to appendicitis.

### COMMENT

*Differential Diagnosis* [3].—Though reliance on these signs is valuable, it has its limitations. Recognition must be given to certain forms of radiculitis which often produce a confusing symptom complex, viz.,

radiculoganglionitis as described by Davis [25] in children or herpes zoster before the rash appears. Radiculitis may occur also secondary to osseous vertebral changes,[26] and subcostal neuritis,[27] secondary to pressure of the twelfth rib on the bony pelvis. Pathologic conditions in the abdominal wall also must be differentiated, e. g., rupture of the right rectus muscle [28] or hemorrhage into the right rectus muscle sheath.[29]

*General Observations.*—Maximal hyperalgesia has been observed to become minimal or to disappear in cases of subsiding appendicitis, after appendectomy and after paravertebral injection.

In several patients with appendicitis operated on by me, the appendix was not located directly under or even in the vicinity of the maximal point of hyperalgesia in the abdominal wall. This is in accord with the opinions of Pottenger,[30] Sherren, Mackenzie and Burgess.[31] The last named studied 500 cases.

In 1 of the cases of acute gangrenous appendicitis there was but slight hyperalgesia of the dorsal eleventh spinal nerve of the right side, although rebound tenderness was present. In comparison with the advanced pathologic findings, the symptoms and the abdominal signs were relatively mild—a not unusual experience in cases of acute gangrenous appendicitis.

A difficulty frequently encountered in diagnosis is the differentiation of retrocecal appendicitis from lesions of the urogenital tract. A comparison of the tender points previously described in diseases of the ureter [32] with those of appendicitis was found to be of value in establishing a diagnosis. Such differential diagnosis is frequently aided by the comparative predominance of the tender points peculiar to appendicitis.

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25. Davis, J. H.: Segmental Neuralgia in Childhood Simulating Visceral Disease, J. A. M. A. **107**:1620 (Nov. 14) 1936.

26. Campbell, W. F.: Surgical Anatomy, Philadelphia, W. B. Saunders Company, 1921.

27. Clinton, M.: Subcostal Neuritis as a Cause of Abdominal Pain, J. A. M. A. **83**:90 (July 12) 1924.

28. Wohlgemuth, K.: Ueber die subcutane Ruptur des M. rectus abdominis und der Arteria epigastrica (spontanes Bauchdeckenhämatom), Arch. f. klin. Chir. **122**: 649, 1922.

29. Danzis, M., and Soschin, S.: Spontaneous Hemorrhage Within Right Rectus Sheath Simulating Acute Appendicitis, S. Clin. North America **6**:1421, 1926.

30. Pottenger, F. M.: Symptoms of Visceral Disease, ed. 5, St. Louis, C. V. Mosby Company, 1938.

31. Burgess, A. H.: An Analysis of Five Hundred Consecutive Operations for Acute Appendicitis, Brit. M. J. **1**:415, 1912.

32. Levitas, M. S.: Tender Points in Diseases of the Renal Pelvis and of the Ureter: Peripheral Distribution of Unilateral and Bilateral Hyperalgesia and Anatomic Relations of the Spinal Nerves and Muscles Involved, Arch. Surg. **39**:457 (Sept.) 1939.

Since the present study is preliminary, further work will be required with a larger series of cases of retrocecal appendicitis before a final opinion can be given.

*Somatic Distribution of the Appendicular Reflex.*—The somatic distribution of the appendicular reflex may be transmitted by way of longitudinal and/or transverse muscle segments in which intersegmental anastomosis of the peripheral nerves may take place. In the thorax there is anastomosis of the intercostal nerves.[33] In the lateral abdominal wall between the transversus and obliquus internus abdominis muscles, anastomosis may take place by way of the lower four dorsal nerves (Hovelacque). I have described likewise such an intersegmental anastomosis of the lower four intercostal and first lumbar nerves, some of which I have found in addition to be intimately connected by way of a plexus formation, looping and nerve termination around the deep circumflex iliac artery.[32] Fusion of the segmental myotomes in the longitudinal posterior muscles, which are supplied by a series of muscular branches derived from the posterior rami of contiguous nerves, has been described.[22] That a similar anastomosis may take place in the posterior muscles of the abdominal wall, viz., the psoas and the iliacus muscle groups, merits study. Davies and associates[34] pointed out that any nerve in the region of the rectus abdominis muscle contains fibers from at least two, and sometimes three, intercostal nerves.

This vast anastomosis of the peripheral nerves in the integral parts of the body wall does not include neuron connections communicating directly with or situated in the spinal cord or communicating with the cerebral centers. Yet, such a wide sensory afferent distribution including the peripheral nerves makes it obvious why in the vast majority of cases of appendicitis the reflex involves more than one spinal nerve.

Mackenzie has on occasion found a distinct segmental nerve distribution as described by Head, but more frequently he has noted an overlapping of nerve segments. In this study, 10 per cent of the cases of appendicitis were found to involve the dorsal eleventh nerve only; in these instances, consideration of overlapping was obviously unnecessary. In the remaining 90 per cent, more than one nerve was found to be involved. In view of this extensive peripheral nerve anastomosis, aside from the other avenues of nerve distribution, it is not difficult to conceive of an overlapping of nerve segments. Sherrington's observation, confirmed by Langley, that there is an overlapping of the segmental skin fields becomes more convincing.

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33. Hovelacque, A.: Anatomie des nerfs craniens et rachidiens et du système grand sympathique, chez l'homme, Paris, Gaston Doin & Cie, 1927.

34. Davies, F.; Gladstone, R. J., and Stibbe, E. P.: The Anatomy of the Intercostal Nerves, J. Anat. **66**:323, 1932.

*Consideration of the Contralateral Reflex.*—In 95 per cent of our cases, a contralateral reflex was elicited. On what physiologic and anatomic basis may this phenomenon be explained? At the midline of the body wall anteriorly and posteriorly there is anastomosis or median overlap between branches of the nerve fibers of the anterior and posterior rami of the spinal nerves of the right and left sides. These nerve fibers are, however, small, and their anastomosis is not extensive. Therefore, it would not be capable of transmitting nerve impulses so intense and far reaching in effect as those observed in this analysis. In visceral disease, the somatic afferent fibers mediate painful impulses from the periphery.[35] Experiments with animals on the conduction of painful afferent impulses in spinal nerves were performed by Ranson and Billingsley.[36] They stated that these impulses must pass through the gray matter and cross to the opposite side of the cord at or near the level at which they reach it. They stated also that Head showed that the same mechanism obtains with reference to protopathic sensibility.

From personal observations, Sherrington concluded that the nociceptive (algesic) impulses are conveyed headward in the spinal cord by way of the lateral columns. Each lateral column conveys such impulses from both lateral halves of the body and, somewhat preponderantly, those from the crossed half, whether these arcs be traced from the skin, the muscles or the viscera. Spiegel,[37] on the other hand, demonstrated in a vascular study that the conduction of afferent impulses from the peripheral vessels in the cat, particularly those which result in painful sensations, is mediated by crossed conduction pathways which are composed of a series of short relays and lie mainly in the ventral part of the lateral funiculi.

The physiologic conception of bilateral conduction in the cerebrospinal nerves in man based on clinical evidence has been herein presented. The inference may therefore be drawn that there exist in man also crossed conduction pathways of the afferent components of the cerebrospinal nerves.

*Hypotheses Concerning Hyperalgesia in the Appendicular Reflex.*—Deductions based on the various observations previously recorded herein have led to the formulation of the following hypotheses:

1. Minimal unilateral hyperalgesia in the appendicular reflex is confined to the eleventh dorsal spinal nerve on the ipsilateral side with occasional anatomic variations.

35. Kuntz, A.: The Autonomic Nervous System, ed. 2, Philadelphia, Lea & Febiger, 1934, p. 471.

36. Ranson, S. W., and Billingsley, P. R.: The Conduction of Painful Afferent Impulses in the Spinal Nerves, Am. J. Physiol. **40**:571, 1916.

37. Spiegel, E.: Ueber das Wesen des Bauchschmerzes und seiner Begleiterscheinungen, Wien. med. Wchnschr. **77**:379, 427 and 456, 1927; cited by Kuntz.[35]

2. Minimal bilateral symmetric hyperalgesia of the appendicular reflex involves the dorsal eleventh spinal nerve on the ipsilateral and contralateral sides. The greater degree is usually found on the ipsilateral side. In this series, in 6 cases out of the 60 (10 per cent), only the dorsal eleventh spinal nerve was involved.

3. In maximal hyperalgesia of the appendicular reflex, two or more consecutive spinal nerves are involved, inclusive of the dorsal eleventh, asymmetrically and bilaterally, the greater intensity and radiation taking place on the ipsilateral side. Conversely, on the contralateral side there is less intensity of hyperalgesia and the radiation is less extensive—a lesser number of nerves being involved than on the ipsilateral side. There is greater spread of radiation above than below the dorsal eleventh nerve, bilaterally. This is anatomically axiomatic. The reaction in the contralateral side is proportionate to the degree of stimulation in the ipsilateral side but to a lesser degree. Comparatively, on either side the dorsal eleventh spinal nerve exhibits maximal hyperalgesia, and to a lesser degree are involved the nerves above and below this level. It is anatomically possible that the anastomosis in the peripheral nervous system may aid in the irradiation of the nerve impulses.

## SUMMARY

The dorsal eleventh spinal nerve unilaterally and/or bilaterally exhibits maximal hyperalgesia and to a lesser degree are involved the nerves above and below this level.

The six points of tenderness along the course of the dorsal eleventh nerve in appendicitis are: (1) in the eleventh intercostal space, elicited by pressure of the examining fingers on the tip of the twelfth rib; (2) in the rectus abdominis muscle slightly mesial to the lateral margin and about on a level with the anterior superior spine of the ilium, and (3) the intersection of a line between these two points and the fleshy margin of the external oblique muscle (frequently located on a level with the umbilicus). There are three points on the right and three on the left side.

Hyperalgesia on the contralateral side was observed in 95 per cent of the cases of proved appendicitis.

The reaction on the contralateral side is milder, and fewer spinal nerves are involved.

This study is based on 60 cases in which the dorsal eleventh spinal nerve was involved maximally on the right side in 55 cases, or 91.7 per cent, and on the left, in 53, or 88.3 per cent.

In 10 per cent of the cases involvement was noted of the dorsal eleventh nerve only, unilaterally and/or bilaterally, while in 90 per cent,

more than one nerve was involved bilaterally. The former have been termed minimal cases and the latter maximal (table 4).

Paravertebral injection of a 2 per cent solution of procaine hydrochloride in the region of the right dorsal eleventh nerve in a case of appendicitis caused pain on the right and left sides to disappear, including that in the chest and in the back. Hyperalgesia likewise disappeared or diminished, and nausea cleared up. A diminished bilateral hyperalgesia of the tender points along the course of the dorsal eleventh spinal nerve likewise persisted.

TABLE 4.—*Typical Cases of Appendicitis with Reference to Hyperalgesia**

| Location | Case 49 (Minimal) | | Case 39 (Maximal) | | Case 33 (Maximal) | | Case 35 (Maximal) | |
|---|---|---|---|---|---|---|---|---|
| | Right Side | Left Side | Right Side | Left Side | Right Side | Left Side | Right Side | Left Side |
| Dorsal 5 | 0 | 0 | 0 | 0 | −+ | 0 | 0 | 0 |
| Dorsal 6 | 0 | 0 | 0 | 0 | +− | 0 | 0 | 0 |
| Dorsal 7 | 0 | 0 | 0 | 0 | 1+ | 0 | 0 | 0 |
| Dorsal 8 | 0 | 0 | 0 | 0 | 1+ | 0 | 0 | 0 |
| Dorsal 9 | 0 | 0 | 0 | 0 | 1+ | +− | +− | 0 |
| Dorsal 10 | 0 | 0 | 1+ | +− | 2+ | +− | +− | +− |
| Dorsal 11 | 1+ | +− | 2+ | 1+ | 2+ | 1+ | 1+ | +− |
| Dorsal 12 | 0 | 0 | +− | +− | 1+ | +− | +− | 0 |
| Lumbar 1 | 0 | 0 | 0 | 0 | 1+ | +− | 0 | 0 |
| Lumbar 2 | 0 | 0 | 0 | 0 | 1+ | +− | 0 | 0 |
| First point: Eleventh intercostal space at the tip of the twelfth rib | 1+ | +− | 2+ | 1+ | 1+ | +− | 2+ | 1+ |
| Second point: Rectus abdominis muscle slightly mesial to the lateral margin and about on a level with the anterior superior spine of the ilium | 1+ | +− | 2+ | 1+ | 1+ | +− | 3+ | 2+ |
| Third point: Edge of the external oblique muscle | 1+ | +− | 2+ | 1+ | 1+ | +− | 1+ | +− |
| Disease of the appendix | Moderate chronic appendicitis | | Chronic appendicitis | | Chronic appendicitis | | Retrocecal gangrenous appendicitis and diffuse suppurative peritonitis | |

* +− signifies very mild hyperalgesia; −+, doubtful or inconstant.

It is believed that the spread of radiation to higher nerve segments may be directly or indirectly concerned with the gastric and pyloric reflexes in appendicitis producing in addition to the diffuse or local pains reverse peristalsis or spasm of the pylorus.

The upper and lower limits of hyperalgesia, bilaterally, are recorded in tables 3 A and 3 B. Comparison of both tables reveals a greater radiation on the right side, extending from the dorsal third to the lumbar second spinal nerves, than on the left.

Retrocecal appendicitis may be differentiated from diseases of the ureter by eliciting the tender points described and noting their predominance over the tender points present in ureteral diseases.[32]

In several patients with appendicitis operated on by me, the appendix was not located directly under, or even in the vicinity of, the maximal point of tenderness in the abdominal wall. This is in accord with the observations of others.

There are longitudinal and transverse muscle segments in the body wall in which intersegmental anastomosis of the peripheral nerves may take place.

On the basis of the clinical evidence herein presented, it may be stated that there apparently exist in man crossed conduction pathways of the afferent components of the cerebrospinal nerves which produce a contralateral reflex.

The classification of the appendicular reflex into minimal unilateral, minimal bilateral symmetric and maximal bilateral asymmetric has been given. Hypotheses have been formulated concerning the modus operandi of the reflex.

Dr. E. D. Congdon, professor of anatomy at the Long Island College of Medicine, contributed the anatomic material used in dissection in these studies and gave advice; my associates at the Israel-Zion Hospital permitted the use of clinical material, and Dr. Frederick Weintraub advised in the preparation of the manuscript.

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# STRANGULATED FEMORAL HERNIA

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Strangulation is the most frequent and most serious complication of femoral hernia. Fourteen per cent of two hundred and twenty-two femoral hernias (31 patients) were strangulated on admission of the patients to the University Hospitals, and an additional 23 per cent had been strangulated on previous occasions. Thirty-two per cent of the patients with strangulated hernias died, and 42 per cent had serious postoperative complications. However, only 1.3 per cent of the patients whose hernias were not strangulated died.

## ETIOLOGIC FACTORS

The small size, the rigidity and the horizontal placement of the femoral ring (fig. 1) account for the frequency of strangulation as well as for the tendency toward early development of gangrene.

Any sudden increase in the intra-abdominal tension may cause strangulation. The most common precipitating factors in the cases at University Hospitals were heavy lifting, excessive straining, vomiting, falling, parturition, constipation and trauma to the abdomen.

Irreducibility, obstruction and inflammation of the hernial contents enhanced the development of strangulation.

The age limits were 86 and 22 years; the average age was 56 years. Strangulation was more common in women than in men and occurred more often on the left side than on the right. Femoral hernia, however, was more common on the right side.

## IMPORTANT PATHOLOGIC CHANGES

A strangulated loop of bowel may become gangrenous and perforate within five hours after the symptoms begin.[1] The area of gangrene may develop as a small spot on the intestinal wall, as an encircling band at the site of constriction or as a purplish black flush involving an entire intestinal loop.

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From the Department of Surgery, State University of Iowa College of Medicine.

1. Watson, L. F.: Hernia, ed. 2, St. Louis, C. V. Mosby Company, 1938.

Owing to the small size of the femoral ring, the hernial sac often admits only a portion of the circumference of the intestinal wall, to constitute a partial enterocele or a hernia of Richter's type (fig. 2). In such a hernia, only the constricted antimesenteric portion of the intestinal wall tends to become gangrenous. Perforations usually occur through the antimesenteric border in either complete or partial enteroceles.

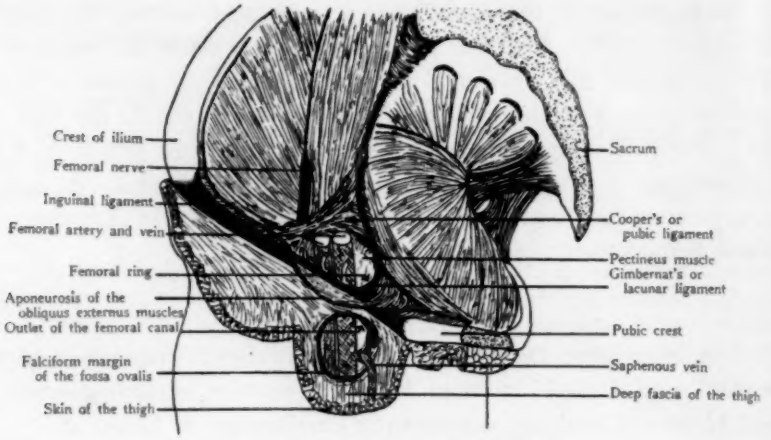


Fig. 1.—The femoral region.

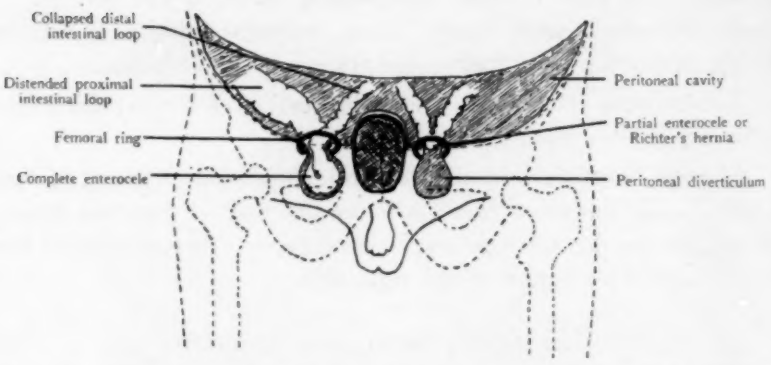


Fig. 2.—Diagram illustrating the mechanism of complete and partial enterocele.

On rare occasions gangrene will involve a portion of the intestine which remains within the abdomen. Such a complication may be caused by extension of the thrombotic process from the vessels of the herniated intestine into the mesenteric vessels of the nonherniated intestine. A similar condition may develop if only the mesentery of the intestine becomes strangulated.

HERNIAL CONTENTS

The small intestine was the more often strangulated. In this series eighteen hernias contained loops of small intestine. These had undergone various degrees of congestion and inflammation but were still viable after being strangulated for periods varying from two hours to seven days. Six hernias contained gangrenous portions of small intestine varying in size from areas 2 cm. in diameter to entire segments 12 cm. in length. The latter six hernias had been strangulated twenty, twenty-four, sixty, seventy-two, one hundred and forty-four and two hundred and forty hours, respectively. In the last case, one of partial enterocele, a spontaneous cutaneous fecal fistula had developed before the patient entered the hospital (fig. 3). Nine, or 29 per cent, of the

Fig. 3.—Photograph showing a spontaneous cutaneous fecal fistula which resulted from prolonged strangulation of a femoral hernia of Richter's type.

strangulated hernias presented partial enteroceles, and three of the nine contained gangrenous small intestine.

A portion of the sigmoid colon containing a large fecalith was strangulated in one hernia for eleven hours. At operation the congested loop was viable and reducible. In this hernia the loop of the sigmoid was probably obstructed by the fecalith before strangulation ensued. Five hernias contained gangrenous omentum, and they had been strangulated for an average period of ten days. The remaining strangulated hernia contained a gangrenous epiploic appendage of sigmoid colon.

Although no similar cases have been recorded at the University Hospitals, such viscera as the urinary bladder,[2] the appendix, the ovary,

2. Vastola, A. R.: Strangulated Femoral Cystocele, Ann. Surg. **97**:724-732 (May) 1933.

the fallopian tube, Meckel's diverticulum, the stomach and the cecum may also become strangulated in a femoral hernia.[1] In one report [3] there was described an embryonic kidney which was present in a strangulated femoral hernia.

### SYMPTOMS AND SIGNS

Most of the femoral hernias were recognized and observed by the patients for several years before strangulation occurred. The average period of observation in this series was five and one-half years; the longest period was twenty-five years. In 6 cases, however, the onset of strangulation was the first indication that a femoral hernia was present.

When the symptoms of strangulation occurred, the patient usually noticed that the hernial mass had become definitely irreducible, firm and tender. The mass no longer transmitted a cough impulse and had increased somewhat in size. The hernial mass was usually located on the thigh beneath the medial extremity of the inguinal ligament (fig. 4), but in 10 cases the hernia was described as lying above the inguinal ligament.

Pain was a constant symptom in the early stages of strangulation. If a portion of the bowel was strangulated, the pain was apt to be sharp and sudden in onset with exacerbations as peristalsis was stimulated. The pains tended to radiate over the abdomen as intestinal obstruction ensued. If only the omentum was involved, the pain tended to be milder, more localized and aching in character. An aching pain, however, did not preclude the possibility of strangulated intestine. The pains continued as long as peristalsis existed. The spontaneous cessation of pain was often a sign that gangrene with paralytic ileus had developed.

Nausea and vomiting invariably followed persistent obstruction of the intestinal tract. These symptoms occurred also in every patient with strangulated partial enterocele or strangulated sigmoid colon. Nausea alone developed in 3 patients with involvement of the small bowel, but the patients were all operated on within five hours. In 1 patient who was operated on within two hours nausea or vomiting did not develop. In 2 patients with strangulated omentum nausea and vomiting developed; in 3, they did not. The strangulated epiploic appendage caused nausea but no vomiting.

Obstipation and distention ensued when the entire lumen of the intestine was obstructed. If, however, the obstruction was in the upper intestine, a considerable quantity of feces and gas was often passed with or without the aid of enemas before obstipation became evident. Although diarrhea may occur with partial enterocele, it was not observed in this series.

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3. Ahrens, P.: Einklemmung des Magens im Schenkelbruch, Zentralbl. f. Chir. **47**:1345-1346, 1920.

The onset of strangulation frequently caused considerable shock and prostration. The pulse rate was usually elevated, and the temperature was often subnormal at an early stage. When shock did not develop or was overcome, the temperature became mildly elevated; it was recorded as 99.6 to 101 F. in 14 cases. When perforation of gangrenous

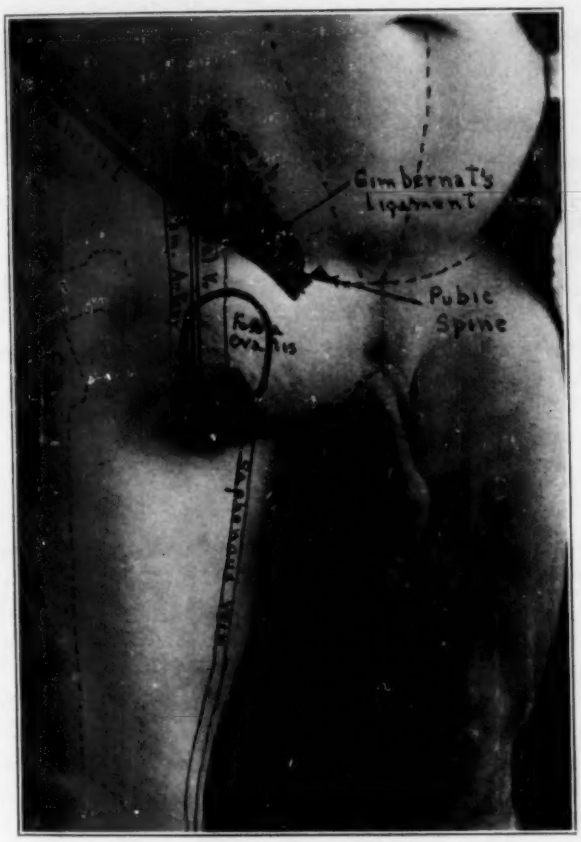


Fig. 4.—Photograph of a large femoral hernia with a sketch of some of the anatomic relations.

intestine occurred or prolonged obstruction developed, ensuing peritonitis instituted a marked septic reaction.

## DIAGNOSIS OF STRANGULATION

The diagnostic difficulties are emphasized by the fact that in this series the average hernia was strangulated for ninety-two hours before the patient was admitted to the University Hospitals.

In 23 of the 31 cases, strangulation was correctly diagnosed on admission. In 3, the anomaly was thought to be strangulated inguinal hernia. In 2, it was called irreducible hernia. In 2, the diagnosis was unexplained intestinal obstruction. In the remaining case, the hernia contained only omentum and was not recognized as being strangulated until the femoral region was explored. In all but the last case, however, operation was performed immediately after the patient entered the hospital.

Three conditions which may increase the diagnostic difficulties are: (1) an aberrant position of the hernial mass; (2) a lack of tenderness or pain in the femoral region; (3) total absence of a visible or palpable femoral protuberance. Difficulties are also encountered in making a diagnosis of strangulated femoral hernia in an extremely old and gravely ill patient since such a patient is often unable to give a lucid history.

The differential diagnosis includes chiefly: strangulated inguinal hernia, thrombophlebitis of the great saphenous vein and femoral lymphadenitis. Rarer conditions are: strangulated lipoma, psoas abscess, distention of the iliac bursa, femoral aneurysm, hydatid cyst, hernia of one of the adductor muscles and strangulated obturator hernia.

## TREATMENT

Immediate operation is the treatment of choice for strangulation of a femoral hernia. Attempts to reduce the strangulated viscera by taxis not only prolong the hazardous delay but add the following possible dangers: reduction en masse without relief of the strangulation; displacement of the hernial mass with consequent confusion of the clinical picture; rupture of the strangulated intestine whether viable or gangrenous; replacement of gangrenous or perforated intestine within the peritoneal cavity; the occurrence of intestinal hemorrhage because of contusion, laceration or ulceration; incomplete reduction with a portion of the strangulated viscera remaining in the sac; the development of paralytic ileus. Furthermore, successful reduction of a hernia by taxis is often only a temporary palliative measure, offering no security against recurrence of the strangulation.

In addition to the preoperative and postoperative care and the repair of the hernial defect, the surgeon is confronted with one or more of four major problems: (1) choice of a surgical approach; (2) selection of the method of reducing the strangulated viscera; (3) accurate examination of the viscera; (4) treatment of gangrenous viscera.

*Surgical Approach.*—There are three possible surgical approaches to a strangulated femoral hernia: (1) through the femoral region; (2) through the inguinal region; (3) through combined lower abdominal and femoral incisions.

An approach from below the inguinal ligament can be carried out rapidly with the least amount of tissue destruction and with the least shock to the patient. The small operative field encourages the use of local anesthesia. The femoral approach, however, offers only the small femoral ring as an exploratory opening through which the strangulated viscera must be delivered for examination and treatment and through which the abdominal cavity may be investigated for additional pathologic changes. Furthermore, the reduction of congested and inflamed viscera through the femoral canal from below is often difficult and dangerous. An attempt to enlarge the femoral ring from below may injure the urinary bladder or sever an aberrant obturator artery.

The inguinal approach can be utilized with a small amount of tissue destruction and shock to the patient, although the procedure is more time consuming than the femoral approach. The floor of the inguinal canal is necessarily opened and offers a fairly large introitus for examining and treating the strangulated viscera and for exploring the abdominal cavity. The inguinal approach offers an excellent exposure of the femoral ring, and any manipulations necessary for reducing the viscera or enlarging the ring can be carried out with all important structures under satisfactory vision. The inguinal incision can also be extended downward to expose the hernial mass from below the inguinal ligament; this facilitates the liberation and reduction of an adherent sac. Local anesthesia can be utilized in most cases, but if general anesthesia is required, a gas anesthetic will give sufficient relaxation. The disadvantage of the inguinal approach is that the floor of the inguinal canal is weakened and must be carefully repaired to prevent later development of an inguinal hernia. However, this exposure of the femoral region enables the surgeon to obtain a higher ligation of the femoral sac and a more adequate approximation of the fascial structures for the repair of the femoral defect.

The combined abdominal and femoral approach consists of two incisions; the first may be either a vertical rectus or a transverse abdominal incision, and the second is the usual femoral incision. Either of the two abdominal incisions offers good exposure of the abdominal cavity and allows the surgeon ample space for examining and treating the involved viscera after their reduction is accomplished. The combined approach is frequently preferred when the strangulation has persisted for a long period, when extensive pathologic changes have occurred in the hernia or when it becomes necessary to explore the abdominal cavity for elusive loops of diseased intestine or strangulated omentum. The disadvantages are that it is time consuming, causes much destruction of tissue, requires general or spinal anesthsia and may cause considerable shock. Since the combined approach is a procedure of

greater magnitude and is utilized for the more serious cases, it is followed by more postoperative complications than either the femoral or the inguinal approach.

In this series the femoral approach alone was used nineteen times, the inguinal approach six times, and the combined abdominal and femoral approach six times.

*Reduction of the Strangulated Viscera.*—Strangulated bowel is often bound to the hernial sac by dense fibrous adhesions which must be removed by sharp dissection. Since the tissues are usually swollen and friable, great care must be exerted not to damage the bowel during the process of separating it from the sac.

After the adhesions are removed, the strangulated viscera can usually be reduced by light pressure from below or by gentle traction on the contiguous structures within the abdomen. A combination of the two procedures is more effective than either pressure or traction alone.

Sometimes the reduction is impossible unless the constricting femoral ring and the neck of the sac are enlarged. The best method of enlarging these structures is to cut medially into the lacunar or Gimbernat ligament. Still greater relaxation of the femoral ring can be obtained by cutting through the inguinal ligament anteriorly, but the latter procedure results in a higher percentage of recurrent hernias despite careful attempts to repair all structures. The recurrence rate is not increased by cutting the lacunar ligament if the incised structures are repaired. In this series the lacunar ligament was cut five times with no recurrence of hernia. The inguinal ligament was incised in 2 cases, in 1 of which hernia later recurred.

*Examination of the Strangulated Viscera.*—After the constricting mechanism is released, the viscera should be withdrawn from the wound and examined for (1) pulsation in the arteries, (2) bleeding from denuded or incised areas and (3) disappearance of the blue-black or purplish color changes. If these signs of returning circulation do not appear immediately, the viscera should be covered with warm moist compresses and inspected at five to ten minute intervals. During the period of waiting the operator should be certain that all points of constriction are completely freed and that no volvulus has occurred. A careful search for minute perforations should be made. The mesenteric vessels should also be examined for possible thrombosis beyond the area of strangulation.

*Treatment of Gangrenous Viscera.*—The successful treatment of a gangrenous intestine consists of two steps: the removal of the gangrenous area and the reestablishment of the intestinal continuity.

A small necrotic area with or without perforation may be treated by inversion into the intestinal wall. The healthy serosa and a tag of

omentum are then sutured over the site of the inversion. A necrotic encircling band may be similarly inverted to produce partial intussusception of the gangrenous material, which subsequently sloughs into the intestinal lumen.

When the gangrenous involvement is too extensive for inversion, the procedure of choice is resection and primary anastomosis. The other alternative is the establishment of an enterostomy with a resultant fecal fistula or artificial anus. Resection and primary anastomosis are imperative if the gangrenous area is high in the intestinal tract, and they are preferable whenever the small intestine is involved unless the patient's general condition prohibits any procedures except simple exteriorization of the diseased loops. Such conditions as extreme intestinal dilatation, generalized peritonitis or gangrenous involvement of several feet of intestine may prevent successful resection and anastomosis. Many surgeons reserve enterostomy for treating gangrenous areas in the descending and the sigmoid colon.

## CAUSES OF DEATH

The mortality rate was 83 per cent among the patients with gangrenous intestine; 50 per cent died because of generalized peritonitis and 33 per cent because of wound infection with septicemia or respiratory complications. The mortality rate among patients without gangrenous intestine was 16 per cent; 2 patients died from cardiac decompensation and 1 from generalized peritonitis due to laceration of a loop of bowel.

The hernias of the patients who died after operation had been strangulated for an average period of eighty-five hours, whereas those of the patients who recovered had been strangulated for an average period of thirty-seven hours. The average age was 66 years for the patients who died and 52 years for those who recovered.

When strangulation occurs, the mortality rate is increased by these factors: (1) a long period of strangulation; (2) gangrene of the strangulated bowel; (3) adherence of the strangulated bowel to the hernial sac; (4) attempts at reduction by taxis; (5) advanced age of the patients.

## RECURRENCES

A follow-up study of all the patients who were treated for femoral hernia revealed that in 23 per cent of those in whom strangulation was present at the time of operation the hernia recurred whereas recurrences developed in only 12 per cent of those in whom hernia had been uncomplicated. One patient had recurrence of hernia and strangulation one year after the first strangulated hernia was repaired, and died as a result of the second strangulation.

## SUMMARY AND CONCLUSIONS

Since the mortality rate was 32 per cent and the recurrence rate was 23 per cent, only 45 per cent of the strangulated femoral hernias were cured by the operative procedures. In contrast, 88 per cent of the nonstrangulated femoral hernias were cured by operation. The occurrence of strangulation evidently caused a 50 per cent decrease in the chances of curing the hernia by operation. It is imperative, therefore, if the surgeon wishes to offer patients with femoral hernia better than a 70 per cent chance of remaining alive and better than a 50 per cent chance of being cured that he fulfil the following demands: (1) Suspect strangulation of every femoral hernia; (2) operate on every strangulated femoral heria immediately after the diagnosis is made; (3) avoid reduction by taxis; (4) carefully select the operative approach which allows adequate exposure for reduction, examination and treatment of the strangulated viscera; (5) preferably use inversion or primary resection for all areas of gangrenous intestine; (6) reserve the procedure of enterostomy for gangrenous portions of the lower part of the colon and for patients who cannot tolerate anything more than simple exteriorization of the diseased loops of intestine; (7) perform early repair of every femoral hernia.

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# STIMULATION OF THE CELIAC PLEXUS IN THE DOG

## I. CARDIOVASCULAR AND RESPIRATORY EFFECTS

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The response to stimulation of the abdominal viscera and the mechanism involved has been a subject of unusual interest and considerable controversy for laboratory and clinical investigators for a long time. Many years ago, Mayer and Pribram [1] and, later, Brodie and Russell [2] observed a rise in the arterial blood pressure with an increase or a decrease in the heart rate following distention of the stomach. Davis and co-workers [3] and Schrager and Ivy [4] in still later reports showed that stretching of the biliary and cystic ducts produced apnea and a variable change in the blood pressure as well as in the heart rate. It was believed that stimulation of the vagus and right splanchnic nerves was responsible for the phenomena observed. Luckhardt and associates [5] noted the appearance of apnea and an immediate fall in the blood pressure following manipulation and traction on the gastrohepatic ligament. While they explained the respiratory effects on the basis of vagal stimulation, they expressed the belief that the circulatory changes were due to mechanical rather than to vasomotor influences. Others showed that traction on the gastric and duodenal arteries is regularly followed by a fall in the blood pressure and/or a reflex vocal cord adduction with laryngospasm or apnea. Recently, Crowley [6] stated in a preliminary report that distention of the small intestine generally produces apnea and an immediate rise in the blood pressure. All of these studies were concerned solely with the stimulation of the viscera

From the Division of Surgery, Department of Anesthesia, New York University College of Medicine.

1. Mayer, S., and Pribram, A.: Sitzungsb. d. k. Akad. d. Wissensch. Math.-Naturw. Cl. **66**:102, 1872.
2. Brodie, T. G., and Russell, A. E.: J. Physiol. **26**:92, 1900.
3. Davis, L. E.; Hart, J. T., and Crain, R. C.: Surg., Gynec. & Obst. **48**: 647, 1929.
4. Schrager, V. L., and Ivy, A. C.: Surg., Gynec. & Obst. **47**:1, 1928.
5. Luckhardt, A. B.; Alpert, R., and Smith, S.: Science **76**:545, 1932.
6. Crowley, R. T.: Am. J. Physiol. **133**:P 253, 1941.

per se and failed to establish the presence of a predominant pattern response following stimulation of the viscera of the upper part of the abdomen.

Since it is established that the viscera of the upper part of the abdomen possess a dual autonomic innervation and that both the vagal and the sympathetic branches contain afferent [7] as well as efferent fibers, a more direct approach to the problem of visceral stimulation is gained by studying the nervous structures concerned. Such studies, which are few, have revealed inadequate and conflicting data. Auer and Meltzer [8] observed a fall in the blood pressure after stimulation of the splanchnic nerve in dogs and rabbits and concluded that the abdominal viscera have a reflex depressor innervation. This phenomenon was observed also in dogs by Burton-Opitz.[9] In the cat, an elevation in the blood pressure followed stimulation of the splanchnic nerve.[10] Laignel-Lavastine [11] observed an elevation of the arterial blood pressure and vasoconstriction of the spleen and the intestine following stimulation of the celiac ganglions in dogs. From the anatomic point of view, Ingersoll established the fact that stimulation of the abdominal viscera produces definite cytologic changes in the celiac ganglion cells.[12]

With the exception of the studies of Laignel-Lavastine and Ingersoll and the preliminary investigations in this laboratory,[13] no other significant report has been found with reference to stimulation of the celiac plexus. Since this plexus with its accompanying splanchnic and abdominal vagal nerves is admittedly the point of convergence for stimuli coming from the viscera of the upper part of the abdomen, it seemed advisable to study the responses to stimulation of these nervous structures rather than of the viscera themselves. Accordingly, it was made the subject of this investigation, and the observed cardiovascular and respiratory effects are hereinafter reported.

## PROCEDURE

Twenty-nine dogs ranging from 9 to 18 Kg. in body weight were used. Premedication with morphine sulfate (2.5 to 5 mg.) and atropine sulfate or

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7. (*a*) Bain, W. A.; Irving, J. T., and McSwiney, B. A.: J. Physiol. **84**: 323, 1935. (*b*) Davis, L. E.: Am. J. Physiol. **59**:381, 1922. (*c*) Harper, A. A.; McSwiney, B. A., and Suffolk, S. F.: J. Physiol. **85**:267, 1935.

8. Auer, J., and Meltzer, S. J.: (*a*) Am. J. Physiol. **31**:21, 1912; (*b*) Zentralbl. f. Physiol. **26**:1316, 1913.

9. Burton-Opitz, R.: Am. J. Physiol. **41**:103, 1916.

10. (*a*) Davis, L. E.: Am. J. Physiol. **60**:560, 1922. (*b*) Sollmann, T., and Pilcher, J. D.: ibid. **30**:369, 1912. (*c*) Davis.[7b]

11. Laignel-Lavastine, M.: J. de psychol. norm. et path. **4**:216-312, 1907.

12. Ingersoll, E. H.: J. Comp. Neurol. **59**:267, 1934.

13. Burstein, C. L., and Rovenstine, E. A.: Circulatory Disturbances Reflexly Inaugurated by Stimulation of Celiac Plexus, Arch. Surg. **35**:599 (Sept.) 1937.

scopolamine hydrobromide (0.05 to 0.1 mg. per kilogram of body weight) was given subcutaneously one hour before anesthesia was induced. Anesthesia was maintained for one to three hours with ether or cyclopropane given by the closed carbon dioxide absorption technic. An endotracheal airway with inflatable cuff was always used. In a few instances, chloralosane[13a] (80 to 90 mg. per kilogram) was employed. Caution was exercised to keep anesthesia uniformly at the second plane of the surgical stage.

Through a left dorsolateral abdominal incision, the celiac plexus was exposed, and the left splanchnic and right abdominal vagal nerves approaching it were isolated from the surrounding tissue. Narrow ribbons of cloth, moistened with physiologic solution of sodium chloride were placed underneath these structures to facilitate handling. The identity of the separate nervous elements was verified by autopsy of all animals used in this investigation.

Carotid arterial tensions and pulse pressures were kymographically recorded with the aid of a mercury manometer; venous pressures were read directly from a calibrated glass tube inserted into the femoral vein. Serial electrocardiograms of lead II with the dogs on their right side were also obtained. Respiratory changes were recorded by a kymograph with the use of a tambour-lever arrangement and a pneumograph placed around the lower portion of the thorax.

Preliminary studies[13] consisting of pulling the stomach, the gallbladder or the duodenum or manually pinching the celiac plexus resulted in a variable response largely due to the lack of control of stimuli employed. It was therefore considered advisable to employ forms of stimulation that could be more satisfactorily controlled. Accordingly, throughout this study the methods of stimulation used were: (1) to apply constant and even tension on the ribbons of cloth placed under the celiac plexus, the left splanchnic or right abdominal vagal nerves; (2) to employ constant faradic stimulation with the aid of a platinum electrode for an average of twenty to thirty seconds to these structures. These were regarded as moderate or strong stimuli. The cardiovascular and respiratory changes obtained were compared with control observations before and after stimulation.

## RESULTS

More than four hundred experimental observations have been made of the cardiovascular and respiratory changes resulting from the application of various stimuli to the celiac plexus, the intact and proximal end of the cut left splanchnic nerve and the right abdominal vagus nerve. These observations have been analyzed and the findings grouped in the following categories:

*Cardiovascular Changes.*—(*a*) Arterial and Pulse Pressures: The effects on the mean arterial and pulse pressures after mechanical and faradic stimulation of these nervous structures are briefly summarized in table 1. It will be seen that although there was some variability in the results, a distinct and predominant pattern response existed following stimulation of the celiac plexus and the intact and proximal

13a. Chloralosane is a preparation of chloralose (a compound of chloral hydrate and dextrose) which has been purified of parachloralose and other impurities.

end of the cut splanchnic nerve. This pattern was characterized by a rise in the mean arterial blood pressure and a decrease in the pulse pressure. It was produced more consistently after faradic than after mechanical stimulation, and, lastly, it was practically absent on stimulation of the intact or proximal end of the cut abdominal vagus nerve (fig. 1). The pattern response remained essentially unaltered following stimulation of the celiac plexus after both vagi were sectioned but was markedly diminished when stimulation followed section of the left splanchnic nerve. The most consistent elevation of the mean arterial pressure and decrease in the pulse pressure were noted after stimulation during anesthesia induced with ether. The absence of pressure changes

TABLE 1.—*Variation in the Circulatory Effects Following Stimulation of the Celiac Ganglion, the Splanchnic and Abdominal Vagal Nerves in Dogs*

| | | Mean Arterial Blood Pressure Changes | | | | Pulse Pressure Changes | | | | Venous Pressure Changes | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Structure Stimulated | Type of Stimulation | Number of Observations | Rise, per Cent | Fall, per Cent | No Effect, per Cent | Number of Observations | Rise, per Cent | Fall, per Cent | No Effect, per Cent | Number of Observations | Rise, per Cent | Fall, per Cent | No Effect, per Cent |
| Left celiac ganglion | Ligature tension | 77 | 59 | 18 | 22 | 77 | 3 | 61 | 36 | 20 | 55 | 15 | 30 |
| | Faradic | 39 | 77 | 5 | 18 | 29 | 0 | 69 | 31 | 7 | 86 | 0 | 14 |
| Left splanchnic nerve | Ligature tension | 48 | 48 | 17 | 35 | 33 | 6 | 36 | 58 | 13 | 54 | 0 | 46 |
| | Faradic | 34 | 79 | 6 | 15 | 30 | 0 | 73 | 27 | 8 | 63 | 0 | 37 |
| Right abdominal vagus nerve | Ligature tension | 30 | 4 | 13 | 83 | 23 | 0 | 22 | 78 | 5 | 60 | 0 | 40 |
| | Faradic | 25 | 20 | 12 | 68 | 20 | 5 | 0 | 95 | 4 | 50 | 0 | 50 |

in a few cases, noted in the table, may be accounted for by the use of inadequate mechanical and faradic stimuli.

The rise in the mean arterial blood pressure ranged from 10 to 90 mm. of mercury (average, 40 mm. of mercury), depending on the type of stimulus employed. It was greater following stimulation of the splanchnic nerve than after stimulation of the celiac plexus and was minimal or negligible when the vagus nerve was stimulated. In over 70 per cent of the observations, the rise in the systolic blood pressure was proportionately less than in the diastolic, with a resulting decrease in the pulse pressure (fig. 1). The decrease in the pulse pressure varied from 4 to 24 mm. of mercury and was followed by a gradual return to normal or, more commonly, by a temporary increase in the pulse pressure. When a fall in the arterial blood pressure occurred (average, 18 mm. of mercury), there was usually an accompanying decrease in the pulse pressure. The pulse pressure was initi-

ally increased in 5 cases, in 3 of which it accompanied a fall in the mean arterial blood pressure.

In all instances, the changes in the mean arterial blood and pulse pressures started abruptly on stimulation and disappeared in one to ten minutes. Occasionally, the initial rise in arterial blood pressure was followed by a slower secondary rise or a compensatory fall.

(*b*) Venous Pressure: Venous pressure readings in 57 instances made during and after mechanical and faradic stimulation of the various

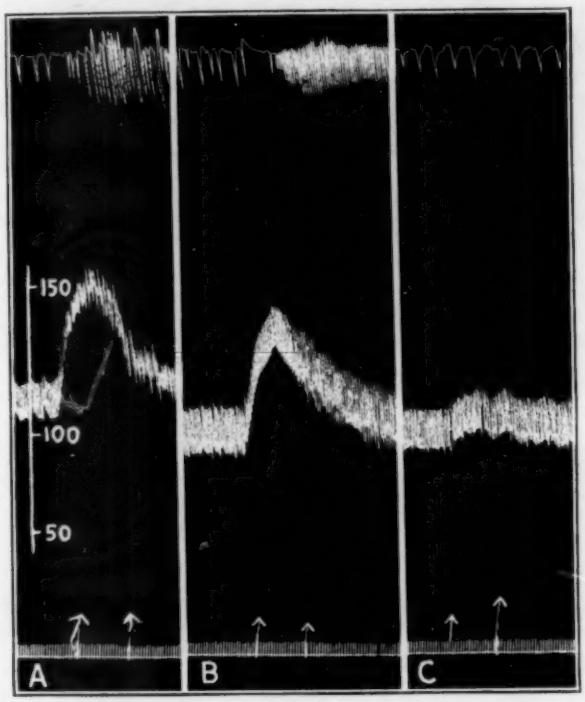


Fig. 1.—Apnea, a rise in the mean arterial pressure and a decrease in the pulse pressure are noted following faradic stimulation of the celiac plexus (*A*) and the proximal end of the cut left splanchnic nerve (*B*) in an etherized dog. Relatively slight effects follow stimulation of the central end of the cut abdominal vagus nerve (*C*). The upper, middle and lower tracings represent respiration, blood pressure and time in second intervals, respectively; the period of stimulation is noted between arrows.

nervous structures showed that if a change occurred, it was usually a rise (table 1). This elevation followed the arterial pressure rise and in all instances was gradual in onset and ranged in magnitude from 8 to 60 mm. of solution of sodium chloride, depending on the type of stimulus employed. Normal levels were reached in one to five minutes.

In 2 instances, a fall in venous pressure followed a decrease in mean arterial blood pressure. In a few cases in which there was no change in venous pressure, there was no variation in arterial pressure on stimulation.

(*c*) Electrocardiogram: In 5 dogs, eighty-three serial electrocardiograms of lead II were taken before, during and after mechanical and faradic stimulation of the various nervous structures. The following significant changes were noted accompanying the elevation in the mean arterial and venous pressures and the decrease in the pulse pressure: The sinus rate was increased (14 to 56 beats per minute), depending on the strength of the stimulus, whenever the celiac plexus or the left splanchnic nerve was stimulated. However, with regard to the abdominal vagus nerve, marked variability in the response was noted. The

TABLE 2.—*Variation in the Respiratory Effects Following Stimulation of the Celiac Ganglion, the Splanchnic and Abdominal Vagal Nerves in Dogs*

| Structure Stimulated | Type of Stimulation | Number of Observations | Initial Apnea Followed by Polypnea, per Cent | Initial Apnea Followed by Gradual Return to Normal, per Cent | Initial Polypnea with Gradual Return to Normal, per Cent | Temporary Decrease in Rate and Amplitude, per Cent | No Effects, per Cent |
|---|---|---|---|---|---|---|---|
| Left celiac ganglion | Ligature tension | 77 | 17 | 48 | 5 | 16 | 14 |
| | Faradic | 36 | 17 | 50 | 0 | 17 | 16 |
| Left splanchnic nerve | Ligature tension | 41 | 27 | 39 | 10 | 10 | 14 |
| | Faradic | 29 | 28 | 38 | 0 | 17 | 17 |
| Right abdominal vagus nerve | Ligature tension | 25 | 8 | 24 | 4 | 8 | 56 |
| | Faradic | 22 | 9 | 18 | 0 | 9 | 64 |

sinus tachycardia was accompanied by a regular rhythm as a rule, and a decrease in the P-R interval, an occasional slight decrease in the QRS time, decrease in the height of the P and R waves, infrequent elevation of the S-T segment and an inversion, decrease or increase in the height of the T wave. Less often, showers of auricular extrasystoles with short runs of auricular flutter occurred. Rarely, there was a slowing of the sinus rate. There were no premature ventricular beats or disturbances in bundle branch conduction. In all instances, the electrocardiographic variations disappeared shortly after cessation of stimulation of the nervous structure.

*Respiratory Changes.*—(*a*) Normal Respiration: Table 2 summarizes the more significant respiratory effects seen after the stimulation of the celiac plexus, the left splanchnic nerve and the right abdominal vagus nerve. It can readily be seen that while such effects were variable, apnea predominantly followed mechanical or faradic stimulation of the celiac plexus and the splanchnic nerve. Apnea was followed by

polypnea (fifty-six to one hundred and twenty minutes) or, more generally, by a gradual increase in rate and amplitude of respiration to the control level. However, stimulation of the abdominal vagus nerve resulted in no change in respirations or, less commonly, in apnea followed by a gradual return to normal rate and amplitude (fig. 1). The appearance of apnea followed by polypnea or a gradual return to normal respiration was not prevented by stimulation of the celiac plexus

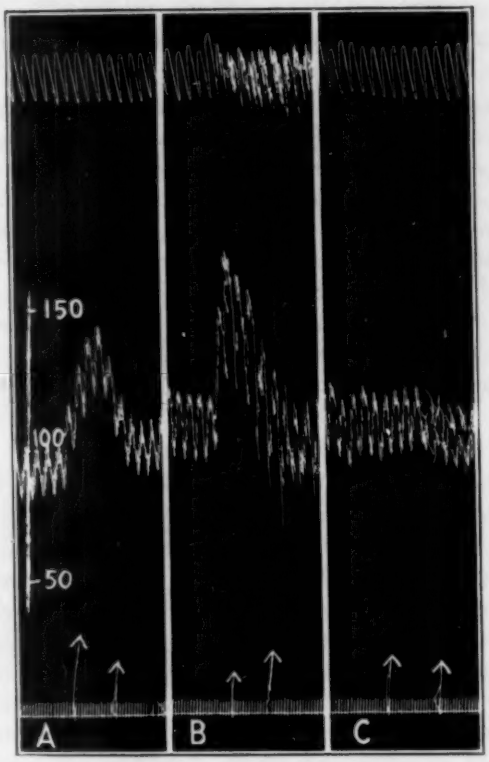


Fig. 2.—During respirations controlled to obviate respiratory changes, the rise in the mean arterial pressure and the fall in the pulse pressure still occur following faradic stimulation of the celiac plexus (*A*) and the cut left splanchnic nerve (*B*). The upper tracing denotes controlled respiration.

after the vagi were sectioned; however, after section of the splanchnic nerve, changes in respiration occurred less often.

The periods of apnea appeared abruptly on stimulation and continued for four to thirty seconds generally in the inspiratory position of the chest. Polypnea, appearing after the apneic periods or initially on stimulation, was characterized also by a marked increase in the

amplitude of respiration. Polypnea was more common and more marked following stimulation of the splanchnic nerve than of the celiac plexus. Rarely, a bizarre pattern of respiration consisting of intermittent and marked changes in both rate and amplitude was noted after stimulation. All respiratory changes disappeared in one to three minutes following cessation of stimulation.

Respiratory effects following stimulation of the nervous structures were more consistent during anesthesia induced with ether and least so when chloralosane was the anesthetic employed. The absence of respiratory changes was associated with no changes in the circulation because of the inadequate stimulus used.

(*b*) Controlled Respiration: Since the predominant apneic interval was found to accompany the characteristic cardiovascular changes on stimulation, controlled respiration by means of a respiratory pump was employed to determine the relation between respiratory and circulatory effects. Seventeen observations made while stimulating the celiac plexus and/or the left splanchnic nerve during controlled respiration revealed a rise in mean arterial blood pressure, although this was not so marked as that obtained during normal respiration (fig. 2); occasionally a fall in pressure was noted. There was, however, no appreciable effect on the decrease in the pulse pressure or the rise in the venous pressure.

## COMMENT

In the literature already cited, there is no agreement as to the effects from stimulation of the viscera of the upper part of the abdomen or of the splanchnic nerve. Our data indicate that a predominant pattern response, characterized by a rise in the mean arterial and venous pressures, a decrease in the pulse pressure, sinus tachycardia and apnea followed by polypnea, can be elicited following mechanical or faradic stimulation of the celiac plexus in the dog. Attention was directed to the plexus and its associated splanchnic and vagal nerves because it is regarded as the region common to most, if not all, of the innervation of the viscera of the upper part of the abdomen.

Consideration of the mechanism concerned with the appearance of this response on stimulation of the celiac plexus has been reserved for a later study.[14] However, it seems from some of the data herein reported that afferent reflex stimulation of the sympathetic system may predominate. This is suggested, in part, by the fact that the cardiovascular and respiratory changes following stimulation of the celiac plexus were not influenced by severing the vagi but were markedly

14. Martin, S. J.; Burstein, C. L., and Rovenstine, E. A.: Stimulation of the Celiac Plexus in the Dog: II. Factors Influencing Cardiovascular and Respiratory Responses, Arch. Surg., to be published.

diminished after stimulation following section of the left splanchnic nerve. The afferent reflex pathway in the splanchnic nerve is apparently more significant in producing such reflex changes than that in the right abdominal vagus nerve. These findings do not substantiate Luckhardt's [5] contention that respiratory changes are due essentially to the stimulation of the vagus nerve and that the cardiovascular effects are dependent on mechanical rather than vasomotor influences following traction of the visceral structures. That associated apnea and/or polypnea are not fundamentally responsible for the appearance of the usual vascular response is borne out by the fact that a rise in the blood pressure with a decrease in the pulse pressure was still noted when the celiac plexus was stimulated during controlled respiration.

Nothwithstanding the appearance of a predominant pattern response following stimulation of the celiac plexus, it must be emphazised that variations in the results were found. While these were few in number, they are significant and are believed to be due to one or more of the following factors: (1) the type and the strength of stimulus; (2) the anesthetic agent; (3) the depth of anesthesia, and (4) species and individual variations. Preliminary studies revealed that manual pinching of the celiac plexus produces no consistent effects on the circulatory system. The use of ligature tension on the nervous structures or faradic stimulation elicited more uniform findings. The data show that weak stimulation of these types commonly produces a fall instead of a rise in the blood pressure. However, moderate or strong stimuli consistently gave rise to an elevation in the blood pressure. This phenomenon may be explained, in part, by the presence of pressor and depressor fibers requiring a weak or a strong threshold stimulus, respectively. Such an explanation has been advanced by Auer and Meltzer [8a] for the splanchnic afferent nerves and by Hunt [15] and Ranson and Billingsley [16] for the somatic afferent fibers.

The anesthetic agent employed is significant in the uniformity of response obtained. The findings obtained were most consistent during anesthesia induced with ether and less consistent when cyclopropane and especially chloralosane were used. It is difficult to account for such observations except to refer to the effects claimed for these agents on the sympathetic [17] or parasympathetic [18] divisions of the autonomic nervous system. As emphasized by Meek,[19] the cardiac arrhythmias

15. Hunt, R.: J. Physiol. **18**:381, 1895.

16. Ranson, S. W., and Billingsley, P. R.: Am. J. Physiol. **40**:571, 1916.

17. Knoepfel, P. K.: Anesth. & Analg. **15**:137, 1936.

18. Adriani, J.; Martin, S. J., and Rovenstine, E. A.: Proc. Soc. Exper. Biol. & Med. **45**:785, 1940.

19. Meek, W. J.: Physiol. Rev. **21**:324, 1941.

noted also may be due to the anesthetic agent employed; according to Rehn,[20] they may result from surgical manipulation.

The influence of the degree of narcosis was eliminated in this study since all animals were carefully maintained in the second plane of the surgical stage of anesthesia. However, the subsequent investigation [14] will point out the significant role of changes in the depth of anesthesia.

The possibility that species or individual differences are responsible for the variations noted has been emphasized. Davis [10a] suggested that the connections of visceral afferent nerves (splanchnic) with the vasomotor center was radically different in the dog and in the cat. The data reported in our study apply for the dog only. Individual animal variation to constant stimuli has been noted not only in different dogs but in the same animal at different times. Evanescent and intermittent changes in the threshold values for stimulation in the viscera are probable even though experimental procedures may otherwise be rigidly controlled.

## SUMMARY

The celiac plexus, the intact and cut left splanchnic nerve and the right abdominal vagal nerve were stimulated in the anesthetized dog with mechanical and faradic stimulation.

It was found that a predominant cardiovascular and respiratory response resulted from such stimulation which was characterized by a rise in the mean arterial pressure, a decrease in the pulse pressure, a rise in the venous pressure, sinus tachycardia and other electrocardiographic changes and inspiratory apnea followed by polypnea or a gradual return to normal respiration.

The pattern response remained essentially unchanged after stimulation of the celiac plexus after the vagus was sectioned; however, it was significantly altered after section of the splanchnic nerve.

Deviations from the pattern response are discussed in the light of various factors, such as the type and the strength of stimulation, the anesthetic agent, the depth of anesthesia and species and animal variations.

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20. Rehn, E., and Reisinger, H.: Klin. Wchnschr. **6**:120, 1927.

# MESENCEPHALIC TRACTOTOMY

## A METHOD FOR THE RELIEF OF UNILATERAL INTRACTABLE PAIN

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Although many neurosurgical procedures have been suggested for the treatment of intractable pain, chordotomy is still the most satisfactory method for the relief of pain in the lower extremities, the abdomen and the thorax. It is not safe when performed in the rostral cervical segments for intractable pain in the upper extremities, owing to the danger of respiratory failure. To avoid this complication posterior rhizotomy has been suggested, but this is undesirable since the upper extremity then becomes anesthetic and useless. This procedure is of more value for the relief of severe pain in the neck. For pain in the arm, the neck and the face, a combination of section of the fifth and ninth cranial nerves and posterior cervical rhizotomy becomes a formidable procedure, especially in a patient who is already debilitated. In such cases Dogliotti [1] suggested section of the lemniscus lateralis in the rostral part of the pons and carried out this procedure in 4 patients. Unfortunately, he has never published his case reports.

From neuroanatomic studies of the spinothalamic and secondary trigeminal pathways,[2] it appears that an equally effective and simpler section of the entire pain fibers from one half of the body including the face may be carried out in the mesencephalon. It has several advantages over Dogliotti's procedure: 1. The site of operation may be reached without retraction of the cerebellum such as is necessary to reach the upper portion of the pons. 2. The incision is made a considerable distance from the superior cerebellar artery and the fourth cranial nerve. 3. It may be carried deeply into the brain stem without damaging such structures as the brachium conjunctivum, which lie immediately below the pain fibers in the upper part of the pons. 4. The landmarks are clearer. It does not seem to have any disadvantages which are not possessed by the other procedure.

In man, the pain pathways from the lower extremities, the abdomen, the thorax and the upper extremities lie on the surface of the mesencephalon

From the Division of Neurological Surgery, University of Chicago.

1. Dogliotti, M.: First Surgical Sections, in Man, of the Lemniscus Lateralis (Pain-Temperature Path) at the Brain Stem, for the Treatment of Diffused Rebellious Pain, Anesth. & Analg. **17**:143-145, 1938.

2. Walker, A. E.: The Spinothalamic Tract in Man, Arch. Neurol. & Psychiat. **43**:284-298 (Feb.) 1940.

just above the lateral sulcus scattered throughout the extent of the lateral lemniscus. In the monkey, the secondary pain fibers from the trigeminal nucleus lie at the level of the lateral sulcus along the lateral margin of the medial lemniscus, and it seems likely that their localization is somewhat similar in the human being. Hence it seemed that a complete section of the pain fibers from the opposite side of the body could be carried out at this level. The procedure was performed on several macaques. In these animals, owing to the preservation of tactile sensibility, hemianalgesia could not be clearly demonstrated. Subsequently the procedure was carried out on 2 patients, both having intractable pain.

## REPORT OF CASES

CASE 1.—*Left mesencephalic tractotomy was performed on a patient with intractable pain on the right side associated with a thalamic syndrome. Right hemianalgesia resulted. Death occurred in twenty-four hours due to cerebral edema. Autopsy was performed.*

E. E., an unemployed married Negro laborer 33 years old, was referred by Dr. George B. Hassin and hospitalized on Aug. 4, 1939. He complained of severe pain on the entire right side of body, including the face, and weakness of the right extremities.

Except for a momentary dizzy spell in September 1938, he was well until March 3, 1939, when suddenly he suffered complete right sensory and motor hemiplegia with aphasia. He became irritable, easily perturbed and angered. His wife stated that it was almost impossible to live with him.

From the time of the stroke he suffered severe pain in the entire right side of the body. It felt as if it were "on fire," "drawing up," "griping," "constricted." Even the weight of bedclothes on the right extremities was unbearable. This pain became worse as the paralysis regressed. It was so severe that he could not put his foot on the floor. The pain or dysesthesia was constantly present but touching the right extremities or rubbing one's hand over them caused intolerable burning.

The patient's personal, familial and systemic histories were essentially irrelevant. He was disoriented in time, place and person, although he knew his own name and recognized his wife.

The cranial nerves were normal except for the following findings: Sensation over the left side of the face was normal. On the right side the threshold for touch was markedly heightened so that even with a 20 Gm. per millimeter Frey hair only about 50 per cent of the stimuli were appreciated. A 1 Gm. per millimeter hair, about the normal threshold stimuli, was not felt at all on the right side, although on the left side about 50 per cent of the trials were appreciated. Pricking the right side of the face caused a peculiar burning sensation with diffuse radiation, even to the right arm and leg. With a 0.5 Gm. Frey pin, seven to ten sticks were required to initiate diffuse burning dysesthesia, which would then last for one to several minutes, gradually becoming more severe and radiating to adjacent areas, at times to the ipsilateral arm and leg. With a 1 Gm. Frey pin about three pricks were required to produce the burning, but with a 2 Gm. pin, a single prick would bring it on. When an 8 Gm. Frey pin

and a tube of ice water were applied to the right side of the face, the patient, blindfolded, was unable to differentiate the two stimuli; both gave rise to burning dysesthesia. Usually irrespective of the type of stimuli, the patient said he was pricked. There was no deviation of the jaw on opening the mouth. The right corneal reflex was diminished. There was a slight weakness in the right lower part of the face, especially pronounced in emotional movements. Hearing was slightly impaired in the right ear for all tones and in the left ear for high tones. Caloric examinations were not made. The right sternocleidomastoid muscle did not contract as well as the left. The right arm was markedly paretic at the shoulder and the elbow and practically paralyzed at the wrist and the finger joints. The right leg was weak, and the ankle and toes could barely be moved. There was marked spasticity in both the right arm and the right leg with lively tendon reflexes and a sustained right ankle clonus. The plantar response was, however, flexor. The abdominal reflexes were absent on both sides. There were no involuntary movements of the right extremities.

Sensation in the right arm and the right leg and the right side of the abdomen was much the same as on the right side of the face. The patient was unable to distinguish between the prick of an 8 Gm. Frey pin and the touch of a tube of ice water, and both caused burning dysesthesia. Occasionally, the pin was said to stick. Even the application of a vibrating tuning fork gave rise to the burning pain. Fine touch was not appreciated on the right arm or the right leg. Position sense was entirely lost. The patient could not even tell which finger or toe was moved. There was complete right astereognosis. With his eyes covered, the patient confused the observer's hand for his own right hand, claiming after feeling the examiner's hand with his left hand that it was his own. He had, however, no difficulty in finding his right hand in space, and he had no illusions of movement of the paretic limbs. He was able to walk in a hemiplegic fashion with the aid of a cane.

Laboratory examinations, including urinalysis, blood studies, studies of sugar tolerance curves, spinal fluid studies and roentgenograms of the skull and the chest, revealed no abnormalities.

On August 15, a small left temporal occipital bone flap was reflected, and after the occipital lobe was elevated, an incision 2 mm. in depth was made from the lateral sulcus to the lower margin of the inferior colliculus. Damage to a plexus of small vessels on the surface caused a small but smart hemorrhage; this was controlled by silver clips. When hemostasis was complete, the bone flap was replaced and sutured.

The patient awoke from anesthesia about five hours after operation. He was too drowsy to cooperate in a detailed examination, but he did not react to pinprick on the right side of the face, the right arm or the right leg, and he did respond on the left side of the body. The following morning he became comatose and about twenty-six hours after operation suddenly died.

A postmortem examination by Dr. W. A. Stryker at 6:00 p. m. on August 16 showed besides the cerebral findings, fatty degeneration of the liver, parenchymatous degeneration of the liver and the kidneys, bilateral pulmonary hyperemia and edema, marked atherosclerosis of the coronary arteries and of the descending aorta, congenital focal fibrous thickening of the left ventricular endocardium, congenital nodule on the mitral valve, primary pulmonary tuberculous complex, focal splenic hemorrhages and lipophages in the mesenteric lymph nodes, the liver and the spleen.

*Neuropathologic Findings.*—The brain stem was soft and edematous and had been lacerated in removal. The vertebral arteries were thickened, and the basilar artery had two hard yellowish plaques in its wall. The internal carotid arteries were thickened, and plaques were present in their walls.

In the posterior portion of the ventral nucleus of the left thalamus was a brownish area of complete softening. Extending posteriorly from this area was a small linear area of softening involving a strip along the medial aspect of the left occipital lobe about 0.5 cm. in width and 2 or 3 cm. in length, which appeared to run into the anterior part of the calcarine fissure.

Serial sections of the thalamus and the brain stem showed that the softening of the left portion of the thalamus had almost completely destroyed the nucleus ventralis posterior of the thalamus and the anterior part of the pulvinar. The softening was complete and surrounding it was a layer of gliosis. The left cerebral peduncle and left pyramid were demyelinized. The medial lemniscus was not so well myelinized on the left side in the pons as on the right side. The basilar artery showed marked intimal thickening with necrosis and fibrosis. Most of the vessels of the brain stem and the diencephalon were thickened. Unfortunately, the laceration of the brain stem at the time of autopsy was so great that the operative lesion could not be accurately delimited.

In this case, which is an example of the thalamic syndrome with somewhat more pronounced motor manifestations than usual, the hemorrhage at the time of operation and the trauma from an attempt to control it were sufficient to cause severe edema of the brain stem, which proved fatal. It is possible to say only that in this case, as far as the results of mesencephalic tractotomy are concerned, the patient appeared to have right hemianalgesia. Before section of the tract, even the slightest pinprick on the right side produced an exaggerated reaction; after the procedure, he did not respond to such stimulation on the right side although he did on the left.

CASE 2.—*Mesencephalic tractotomy was done on a patient with carcinoma of the tongue with regional metastases producing intractable pain in the right side of the neck and the face. The results were complete relief of pain, right hemianalgesia and hemithermanesthesia. Death occurred in one month. Autopsy was performed.*

A. V., 57 year old spinster, was referred to the neurosurgical service on April 3, 1941 because of severe intractable pain on the right side of the neck as the result of carcinomatous metastases from the tongue to the regional lymph glands. Three and a half years previously she had noticed a lump on the left edge of the tongue. This was removed and diagnosed as carcinoma. Recurrence developed two years later. Radium needles were inserted at this time. One month later, 3,825 roentgens (r) was given. In December 1939, recurrence was found at the margin of the former lesion, and partial glossectomy was performed with radical removal of the glands of the left side of the neck. In May 1940, still more radical extirpation was attempted after splitting the mandible in the midline. Since the last operation she had suffered considerable soreness and tenderness over the right side of the jaw and was unable to open her jaw more than 1 or 2 cm.

On March 19, 1941, another attempt was made to excise carcinomatous nodes on the right side of the jaw. The neoplasm, however, extended beneath the base of the skull and to the wall of the carotid artery. Following this last operation, she required morphine, phenobarbital and codeine daily in varying amounts. At the time of transfer to the neurosurgical service the patient was complaining of pain in the right submaxillary region radiating to the right occiput. Occasionally sharp shooting pain was present on the right side of the face.

The patient was cooperative, but her speech was difficult to understand owing to inability to open the mouth and the previous operative procedures on the tongue. There were no obvious deformities of the head. She held the neck rigidly. There was a large pack in an open wound in the right submaxillary region. The cranial nerves were normal except for a fine horizontal nystagmus on looking to the right and the left and the difficulties resulting from the previous operations on the tongue and the jaw. Cotton contact and pinprick were well appreciated over the entire face. Both corneal reflexes were active and equal.

The motor and sensory system were normal for a woman of her age and debility. The patient was unable to walk and had not done so for several months. An attempt was made to test her sensation with Frey hairs, but owing to her difficulty in talking and the obvious pain from which she suffered it was impossible to obtain accurate results.

On April 4, with the patient under anesthesia induced with avertin with amylene hydrate, mesencephalic tractotomy was carried out on the left side. A left posterior temporal osteoplastic craniotomy was made. The dura was opened with a horseshoe-shaped incision, the toe being cut along the lateral sinus. It was reflected upward. A group of small veins passing to the lateral sinus were coagulated and cut. The lateral surface of the temporal lobe was then elevated, and the tentorium cerebelli was incised to the incisura. The mesencephalon covered by arachnoid was thus exposed and the superior cerebellar artery visualized in the angle between the cerebellum and tectum mesencephali. The area was vascular, but eventually the arachnoid was separated from the vessels and retracted from the lateral surface of the mesencephalon. A special Bovie point having a lead marker 3 mm. from the end was then tested on the cerebellum, and when the strength of the current sufficient to cut readily had been obtained, it was plunged into the mesencephalon near the rostral margin of the inferior colliculus at the lateral sulcus. When the current was applied, the patient jerked, and a second cut was necessary to complete an incision toward the inferior colliculus for a distance of approximately 6 mm. The upper edge of the incision was at the ridge on the brachium of the inferior colliculus. There was no bleeding. Approximately ten seconds after the section, the patient stopped breathing for a few seconds, and then the normal respiratory rhythm was resumed. The bone flap was replaced, and the skin was closed in the usual manner.

The patient woke from the anesthesia and responded feebly four hours after the operation. She was able to move all four extremities. The right corneal reflex was absent; the left was active. On the first day after operation the patient was more responsive, complained of no pain, was able to speak in a whisper almost as well as before the operation and had no evidence of aphasia. There was suggestive right homonymous hemianopsia. Pinprick was not appreciated on the entire right side, and the right corneal reflex was absent. The pupils were 2 mm. in diameter and did not react to direct light. External ocular movements were full. Both plantar reflexes were flexor. The wound in the neck was dressed without producing any discomfort—a procedure which before the operation was agonizingly painful to the patient. She had some difficulty in

swallowing. On the third postoperative day the patient had no particular complaints. She carried out finger-nose and heel-knee tests well on the two sides. The grip was poor but equal on the two sides. There was right hemianalgesia except for a slight appreciation of pinprick on the right leg. Position sense of the right hand was intact. She showed no evidence of aphasia.

On April 10, six days after operation, she was examined in detail. She complained of no pain except at the site of the cerebral operation. Both pupils were small but reacted well to direct and consensual light. External ocular movements were full except for limitation of the upward gaze. The right palpebral fissure was larger than the left. There was no facial weakness. The right corneal reflex was absent and the left present. The right side of the face was practically analgesic. The patient appreciated pinprick on the right side only occasionally and then considered it much duller than on the left side. Heat and cold were occasionally appreciated as such on the right side of the face. The line of division between normal and abnormal was slightly to the right of the midline. Touch was equally keen on the two sides, and tickle was the same on the two sides. Pinprick appeared to be appreciated on both sides of the tongue, but owing to the partial glossectomy, it was difficult to be certain that the anatomic right side of the tongue was being stimulated. Hearing, as tested by the spoken voice and tuning fork of 128 cycles per second, was normal bilaterally. Swallowing was difficult. The patient's voice was husky but not much different from what it was before operation. The tendon reflexes were active throughout. Both plantar reflexes were flexor. The abdominal reflexes were absent bilaterally. Pinprick was appreciated occasionally on the right leg but not at all on the abdomen, the thorax or the right arm. The division between normal and abnormal seemed to be slightly to the right of the midline over the chest and the abdomen. Cotton contact was appreciated well over the trunk and the upper extremities, although it was occasionally missed on both legs. Position sense was intact throughout. Vibratory sensation was slightly but equally decreased in both legs and normal in the arms. Stereognosis was slightly but equally impaired in both hands. The patient did not appreciate heat or cold on the right arm and only occasionally on the right leg. She was able to move all four extremities through a full range of movement. Coordination and muscle tone were normal.

On April 20, the patient began to have so much difficulty in swallowing that tube feeding was instituted. At this time, peripheral right facial weakness was noted. The patient was comfortable, although occasionally she complained of aching in the right arm, which was relieved by massage.

On April 23, her condition was much the same as previously. Right hemihypalgesia was present, but there was increased appreciation of pinprick and temperature below the midthigh on the right leg, although these modalities were not appreciated normally in this region. The strength was good in all four extremities. The tendon reflexes were active and equal.

Metastatic nodules were felt in the left submaxillary region on April 27. The patient complained of pain in the neck and aching in the region of the right shoulder. Breathing became more difficult due to tracheal obstruction, and the patient was apprehensive. For the first time since the mesencephalic tractotomy, she was given morphine. By that means she was kept in a stuporous condition until she died of bronchopneumonia on May 1.

*Neuropathologic Findings.*—Permission was given for examination of the head. On removal of the calvarium, the brain appeared grossly normal with the exception of a wide incision on the lateral surface of the left mesencephalon. The

lower end of the incision was at the lateral sulcus, approximately 4 mm. from the anterior margin of the brachium pontis. It was 2 or 3 mm. in width and extended dorsally across the lower margin of the brachium of the inferior colliculus in the direction of the caudal extremity of the superior colliculus. The incision was 7 mm. in length (fig. 1). The temporal lobe appeared normal, and there were no softenings.

Serial sections were made of the rostral portion of the pons, the mesencephalon and the caudal part of the diencephalon. They were stained for cells by Nissl's technic and for myelin by the Smith-Quigley method. The lesion was seen to begin near the caudal border of the mesencephalon as a triangular zone, the lower margin of which pierced the lateral sulcus. It extended inward for a distance

Fig. 1 (case 2).—Photograph of the lateral surface of the mesencephalon after removal of the occipital lobe, the cut surface of which is seen at the left. The lesion is marked in black; *BP*, basis pedunculi; *CC*, corpus callosum; *I*, brachium colliculi inferioris; *SA*, arteria cerebelli superioris; *SC*, colliculus superior; *SL*, sulcus lateralis mesencephali; *IV*, nervus trochlearis.

of 5 mm. At this point the medial lemniscus was inferior to the lesion, but the fibers of the lateral lemniscus were sectioned with the exception of a few lying along the superolateral margin of the inferior colliculus. Traced anteriorly, the lesion was seen to maintain its lateral portion, its inferior border following the lateral sulcus. It extended into the mesencephalon for a distance of 1 cm. at the junction between the inferior and the superior colliculi (fig. 2). It had destroyed the inferior portion of the spinothalamic and spinotectal tracts, the brachium of the inferior colliculus, a part of the central tegmental pathway and

the most dorsal portion of the medial lemniscus, including the secondary trigeminal tract. It did not involve the fibers of the brachium conjunctivum or the fibers of the third nerve. The most anterior portion of the lesion extended to the junction of the medial geniculate body and the mesencephalon, destroying at this level a few fibers of the lateral and medial lemnisci.

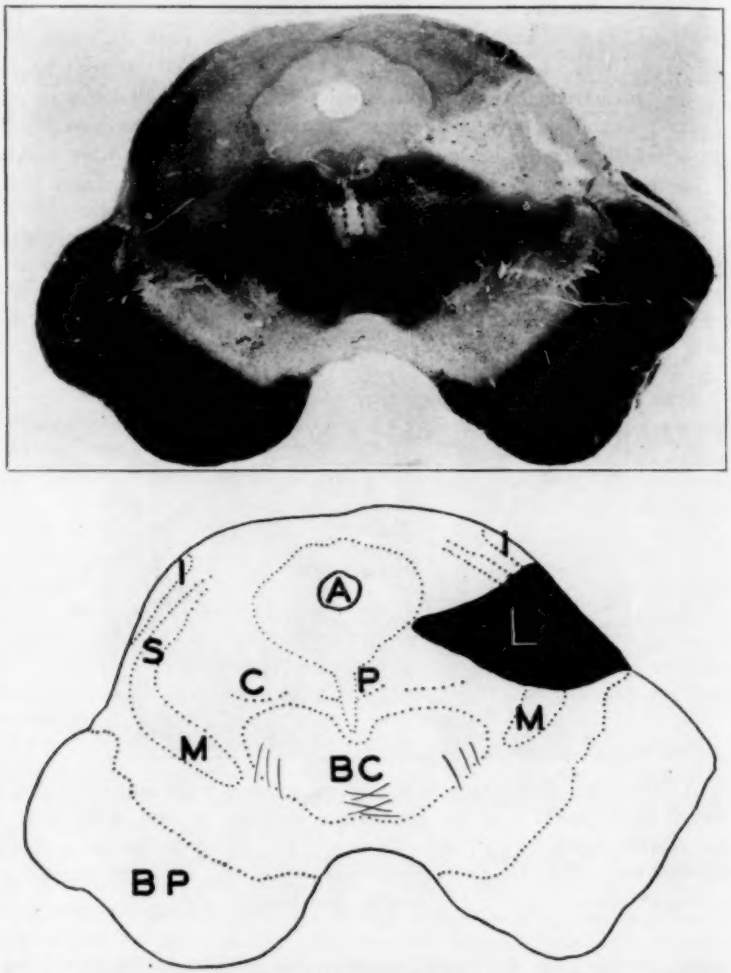


Fig. 2 (case 2).—An untouched photomicrograph of a section at the point of maximum damage to the mesencephalon (immediately caudal to the superior colliculus) and a sketch of the section with the tracts labeled: *A*, aqueductus sylvii; *BC*, brachium conjunctivum; *BP*, basis pedunculi; *C*, tractus centralis tegmenti; *I*, brachium colliculi inferioris; *L*, lesion; *M*, lemniscus medialis; *P*, fasciculus longitudinalis medialis; *S*, tractus spinothalamicus. The section was stained by Smith-Quigley technic for myelin; × 3.

In this case, mesencephalic tractotomy gave complete relief from intractable pain in the neck without producing evidence of motor or pro-

prioceptive impairment of the extremities. It is impossible to say that this patient had no neurologic defect other than the loss of pain and temperature on the right side because she was unable to be on her feet. It is possible that she might have exhibited unsteadiness on walking had she been strong enough to stand. However, she did not complain of any weakness. She did notice at times an aching in the right arm, and she did state that the right arm did not feel normal, but this was only when she touched it with the left hand. The right arm could be used for normal purposeful movements.

## COMMENT

These cases demonstrate the feasibility of differential section of the pain and temperature pathways at the level of the mesencephalon preserving the tactile and the proprioceptive fibers. Although technically the procedure is not extremely difficult, it is not one to be undertaken lightly owing to the danger of hemorrhage in a restricted field. The operation has a considerable mortality, although this may become less as one gains familiarity with the procedure. At times it may not be possible to attempt the section because of the vascular plexuses about the mesencephalon. In 1 case the attempt was abandoned after finding the mesencephalon almost completely covered with vessels and distorted by the local lesion. When successful, however, the procedure will completely relieve unilateral intractable pain without impairing the motor function of the extremities or producing annoying subjective paresthesia.

*Topical Localization of Pain Fibers in the Mesencephalon.*—The second case allows limited conclusions regarding the topical localization within the spinothalamic tract. It has previously been suggested [2] that the fibers of the spinothalamic tract from the lower extremities lie superiorly to those from the trunk and the upper extremity at the level of the mesencephalon. In the second case the appreciation of pain and temperature returned to a considerable degree in the lower extremity. This sparing is presumably due to the intact superior portion of the spinothalamic tract. The general somatotopical arrangement of the pain fibers at the mesencephalon would then be from dorsal to ventral—leg, abdomen, arms and face. In order to obtain complete hemianalgesia, the incision must be carried from the lateral sulcus to the superior margin of the brachium of the inferior colliculus.

*Secondary Trigeminal Pathways.*—Neuroanatomists have been uncertain of the secondary trigeminal pathways owing to conflicting experimental reports. As a result of the studies of Wallenberg [3] and

3. Wallenberg, A.: Secundäre sensible Bahnen im Gehirnstamme des Kaninchens, ihre gegenseitige Lage und ihre Bedeutung für den Aufbau des Thalamus, Anat. Anz. **18**:81-105, 1900.

van Gehuchten [4] on rabbits, it was considered for many years that the dorsal secondary trigeminal tract conveyed fibers from the spinal nucleus of the trigeminal nerve. This bundle of fibers lies in the reticular substance just lateral to the posterior longitudinal fasciculus in the upper portion of the pons and the mesencephalon. Recent experimental evidence has cast doubt on this hypothesis.[5] The present study makes it still less likely, because the dorsal secondary trigeminal tract was not damaged in case 2, in which the face was practically analgesic on the right side. The secondary pathway from the spinal trigeminal nucleus lies in the lateral portion of the medial lemniscus and reaches the surface near the lateral sulcus of the mesencephalon. Since these fibers were damaged by the lesion in case 2, the conclusion that they represent the secondary pathways from the spinal nucleus of the trigeminal nerve seems justified.

*Corneal Reflex.*—It is of interest to note that the corneal reflex was diminished in the first patient before operation as the result of the thalamic lesion. (Serial sections of the brain stem showed no lesion of the fifth or seventh cranial nerves or their nuclei.) In the second case, the corneal reflex was practically absent after mesencephalic tractotomy, and in this case serial sections of the brain stem failed to show a lesion of the nuclei of the fifth or seventh cranial nerves. It is therefore evident that there must be a suprasegmental arc for the corneal reflex. This cerebral arc of the corneal reflex has been demonstrated and discussed previously.[6] The present cases present evidence suggesting that the afferent limb of this reflex arc consists of fibers of the secondary trigeminal tract passing with the spinothalamic fibers.

## SUMMARY

A method is described for the differential section of the sensory pathways in the mesencephalon. The pain and the temperature fibers are cut, leaving intact the tactile and the proprioceptive fibers. Such a section will give relief from unilateral intractable pain without producing paralysis or numbness.[7] Two cases in which the operation was used are described.

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4. van Gehuchten, A.: Recherches sur les voies sensitives centrales, La voie centrale du trijumeau, Névraxe **3**:235-261, 1901.

5. Walker, A. E.: The Origin, Course and Terminations of the Secondary Pathways of the Trigeminal Nerve in Primates, J. Comp. Neurol. **71**:59-89, 1939.

6. Walker, A. E.: The Cerebral Arc of the Corneal Reflex, J. Nerv. & Ment. Dis. **92**:569-578, 1940.

7. Since this paper was submitted for publication, mesencephalic tractotomy has been performed for intractable pain in 3 additional cases without an operative death. Two patients stated that the contralateral half of the body felt dead, and 1 of these had a disagreeable but not painful sensation in the affected arm at times. All 3 were relieved of pain.